Neuromuscular Disorders

A Comprehensive Review with Illustrative Cases

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Foreword

There have been many great scientific discoveries in recent years in the elucidation of the aetiology and pathogenesis of a wide range of neuromuscular disorders. These advances are mainly due to the power provided by modern DNA technology applied to the inherited diseases and by the new discoveries in immunology directed to the acquired conditions. Many novel diagnostic tests have been derived from this research much to the benefit of the patient.

However the clinician should not be distracted by the glamour of these new tests away from the primary role of clinical evaluation at the bedside. The patient's history and the physical examination remain foremost in medical practice ensuring that the laboratory advances are placed in the correct context. The care of a patient with a neuromuscular disorder begins with the clinical workup followed by the relevant laboratory tests and electrophysiological assessment where indicated. It is a tribute to the authors that they have highlighted this basic principle in the book which is strongly clinically oriented. At the same time, the most recent advances arising from DNA technology, immunology and histochemistry in neuromuscular research have been well-integrated into the clinical arena. In this way, the new book fulfils a very timely need.

DNA analysis provides an exact genetic diagnosis for the many inherited myopathies and neuropathies and is especially useful in distinguishing conditions which share the same phenotype, e.g. Becker muscular dystrophy versus Kugelberg–Welander proximal myopathy with calf enlargement. Thus the primary myopathies are clearly distinguished from the neurogenic conditions. Apart from the genetically determined disorders, there is also a wide range of neuromuscular diseases which have an immunopathogenetic basis.

The book written by senior, experienced experts in the field is presented in sections devoted to each of the major neurological manifestations which are assembled in logical order. A novel and useful part of each chapter ending is a discussion of key points presented in an educational style as a teaching aid in the investigation and treatment of the conditions under consideration. Despite the complexity of the subject, the book is 'reader-friendly' and presents itself as a valuable learning tool. The work is directed both to the postgraduate trainee and to the clinician who wishes to be informed on recent developments so that it is of use to all who are concerned with neuromuscular disorders, either as neurologists, physicians or general practitioners.

The book fulfils its stated objective of being both a learning tool and a source of information concerning the latest developments in neuromuscular research within the clinical realm. As such it is highly recommended as an excellent guide for the diagnosis, management and treatment of neuromuscular disorders.

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Preface

The purpose of a book is to provide an interesting learning tool for students and practitioners. This is challenging in the current times where we have seen an explosion of medical knowledge and enormous literature has emerged in the field of neuromuscular disorders. This is largely due to advances in immunohistochemistry and genetics. Disease mechanisms are becoming clearer and therapies may well emerge in the near future. A new entrant to the field is likely to find himself bewildered with the datasets, and more than ever, sound clinical foundations have become necessary. This book is clinician-friendly and aimed at providing structured information of the large assortment of neuromuscular disorders.

The table of contents has been designed for the convenience of the clinician and hence divides the areas into clinical scenarios, commonly encountered in consulting rooms or the wards of hospitals. Thus, the chapters cover pure motor diseases, sensorimotor diseases, sensory diseases, fluctuating diseases and so on. Each chapter follows a conventional pattern, and tables have been provided for ease of remembering. Illustrative cases from authors' clinical experience have been included, which elucidate some of the points made in the foregoing discussions. Each chapter ends with key points (when to suspect, how to investigate and how to treat) for revision and quick reference. While the book provides up-to-date information and is heavily referenced, it is neither too lengthy nor difficult to read and assimilate.

The preparation of the book took almost one and a half year. In this time, we three authors (Satish V. Khadilkar, Rakhil S. Yadav and Bhagyadhan A. Patel) had different work stations and differing roles to adapt. The editing process went on simultaneous to the writing of chapters and finalising on the cases to be included. This was also an eventful time for all of us; Bhagyadhan A. Patel had a change of his workplace and designation, Rakhil S. Yadav had the good fortune of fathering his second child, and Satish V. Khadilkar shifted his university position from the Grant Medical College and Sir J.J. Group of Hospitals to the Bombay Hospital Institute of Medical Sciences.

Senior colleagues helped by reaffirming the need for such a book and giving timely advice on formats. Interactions with neurology residents and younger colleagues were very important for us to decide the formulation of chapters. People at

Springer have been very friendly and competent, enticing us throughout the publishing process.

A special mention of Prof. Byron Kakulas, an authority in the field of neuromuscular disorders, is a must. He has been the guiding force for Satish V. Khadilkar. He kindly agreed to write the foreword for this book, for which we are indebted to him.

We are indeed grateful to our families for graciously bearing with us, to all our students and colleagues for their help and constructive comments and to all our patients for whom these activities exist.

We do hope that readers will find this book useful in their preparations for various examinations and practice of neuromuscular disorders.

Mumbai, Maharashtra, India — Satish V. Khadilkar
Ahmedabad, Gujarat, India — Rakhil S. Yadav
Mumbai, Maharashtra, India — Bhagyadhan A. Patel

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Statement on Consent and Ethics Committee

To whomsoever it may concern,

This is to state that we, the authors of the book *Neuromuscular Disorders: A Comprehensive Review with Case Illustrations*, are in possession of consents from the patients or their families to publish their data and photographs, particularly in situations where individuals are identified.

We also state that ethics committee approval is not applicable to this project as it does not involve any experimentation with human subjects.

13 June, 2017

Satish V. Khadilkar
Rakhil S. Yadav
Bhagyadhan A. Patel

About the Authors

Satish V. Khadilkar, M.D., D.M., D.N.B.E., F.I.A.N., F.A.M.S. is one of the first few Indian neurologists to have pursued the subspecialty of neuromuscular disorders, a field in which he has made a mark in India and beyond. He was the first to describe a new clinical sign, the 'hip abduction sign', which has since been included in international books. He contributed the first Indian accounts of sarcoglycanopathies and dysferlinopathies and was instrumental in finding the founder gene in calpainopathies in Agarwal community and the founder mutation in GNE myopathy in inhabitants of Rajasthan. He presently represents India at the Asian Oceanian Myology Center.

He has twice been honoured with the Best Teacher Award by Grant Medical College. His lecture series for M.D. students has been very popular and has been converted into digital teaching material, which is distributed free of charge. He has authored over 150 publications and has written 4 books and edited one on neurology. He has also been active in social work, serving as the trustee and secretary of the Muscular Dystrophy Society and as the national vice president of the Multiple Sclerosis Society of India. He has received prestigious fellowships from the Indian Academy of Neurology, Indian College of Physicians and National Academy of Medical Sciences.

Rakhil S. Yadav, M.D., D.M. passed his D.M. in neurology from the prestigious Grant Medical College and Sir J.J. Group of Hospitals and worked further as lecturer in the same department. Subsequently, he trained in neuromuscular disorders at Paris. He is presently working as a consultant neurologist at Ahmedabad. He has been a faculty of neuromuscular symposia, is associated with the *Annals of the Indian Academy of Neurology* and has contributed and participated in various book chapters and peer-reviewed indexed publications. He has also been ICMR project guide.

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(IAN) Summer School Quiz (2015 and 2016) and IAN-Bar-B-Quiz (2015). He has presented many papers, posters and cases at various national-level conferences. He has published articles in international journals. He is actively involved in teaching programmes for postgraduate students in neurology and internal medicine. He has a special interest in neuromuscular disorders.

Neuromuscular Disorders: A Clinical Approach

1

1.1 History and Examination in Neuromuscular Disorders

History taking in neuromuscular disorders, while similar to other areas of neurology, has some special aspects which need to be borne in mind. Patients are often suffering for long, and their disabilities may have led to negative or difficult attitudes. It therefore pays to go that extra length in connecting with the patient and the family before beginning the interview. This is perhaps a very important step, as the physician has to carry them through the protracted and difficult process of achieving the precise diagnosis, explaining the limited availabilities at the disposal, to help them lead as productive a life as possible and to discuss and guide through the preventive aspects of these chronic and limiting diseases. The interviews can get lengthy as a lot could have happened in the patient's life before he has reached you; this is particularly true in countries where the expertise and resources are in short supply. It is useful to schedule the clinical interview early in the day so that the tests could follow on the same day. This means a lot to the disabled individuals and their caregivers. On the other hand, sometimes the first examination may have to be performed in the intensive care unit and will have limitations of the patient's ability to cooperate and the rigmarole of the intensive care units.

The exercise of diagnosing the patient's condition from his own words is rewarding as it cuts the costs of investigations. Hence listening to the patient while he speaks (without 'using' that time to fill out forms) helps formulate the diagnostic process. Regrettably, as we 'advance' in medicine, the number of things to arrange, beyond the clinical examination, are ever increasing and that is likely to derail the young doctor into allowing his mind to get distracted from the patient's account of his illness. Once a symptom is given, it should be pursued in its entirety by asking questions to determine the duration, areas affected, associated features, exacerbating and relieving factors and, importantly, whether the issue is progressing or improving. Due to chronicity, some landmarks tend to get hazy, and helpful suggestions from the examiner will clarify the confusions.

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1.1.1 Family History

Family history assumes much importance in neuromuscular disorders as a large proportion of these diseases are inherited in nature. Neuromuscular conditions can have intra-familial 222variations and formes frustes exist, and hence it can be difficult for families to correlate the basis of differing manifestations seen in family members and they may not be reported. For example, in a multisystem disease like myotonic dystrophy, relatives can have early cataracts, frontal baldness, infertility or diabetes which are unlikely to be perceived as parts of the muscular illness of the index case. A condition like facioscapulohumeral dystrophy is known to have increasing severity in successive generations, the anticipation. Mild sufferers in the earlier generation with facial weakness or scapular winging could have gone through life without much disability and not come to medical attention. In families having hereditary neuropathies, pes cavus may be considered as a family trait and passed off as 'we all walk like that' and not linked with the neuropathy. Mitochondrial disorders frequently have pleomorphic manifestations within a family, and the manifestations range widely from muscular weakness to cerebellar ataxia to visual failure and are hence interpreted as independent issues. In conditions which manifest late in life, for example, oculopharyngeal muscular dystrophy or frontotemporal dementia with amyotrophic lateral sclerosis, individuals in a given family may not have reached the age of manifestation but could harbour the traits. Hence depending upon the nature of the symptoms and signs of the proband, it is important to ask relevant questions and to draw the detailed family tree for better understanding of the disease process. Often, information of three generations is not clearly available. In such a situation, if a vertical transmission is seen, pseudodominant pattern of an autosomal recessive condition should be kept in mind as recessive conditions far outnumber the dominant ones. It is also important to include both the paternal and maternal sides of the family in the inquiry. While this states the obvious, in some cultures, maternal side of family is considered separate. Also, in a condition like Duchenne muscular dystrophy, a mother may have lost her brother early on, and she may not bring it up as implications can be negative in some situations. Populations vary in their marriage customs, and community marriages are common in many parts of the world. When the members of a given community are few, genetic admixture is inevitable and the situation really is of intra-communal exogamy. Thus, a careful family history can be of much help in the diagnostic process.

For ease of reading, symptoms and signs of neuromuscular diseases have been discussed together in this chapter.

1.1.2 Gait, Stance and Posture

The diagnostic process begins as soon as the interaction starts. Changes in gait, stance and activities are most visible as the patient enters your room, not knowing what to expect. As he or she familiarises with the surroundings, corrective actions come into play, masking some signs. Individuals with severe proximal weakness

may prefer to stand throughout the interview in order to avoid the embarrassment and difficulty of not being able to rise from chair. Similarly, weak patients may not want to climb onto the examination bed by using the step, instead preferring to stand close to the table, facing away from it and pushing themselves on to the bed by using their arm strength. Observing the patient as he stands and walks can give very useful information as to which muscles are likely to be weakened. The face will be expressionless and smile incomplete when facial muscles are weak. Patient may support a weak neck or jaw. Patients with myasthenia and motor neuron disease sometimes use the strength of digits to move the lower jaw as they talk. Cervical collar may be worn to help stabilise the neck. When the interscapular muscles like the rhomboids and trapezius are weak, scapulae slide forwards and outwards so that the whole upper limbs are rotated in such a way that dorsum of the hands face forwards at rest. This changes the pattern of arm swing. Lordosis and protuberant abdomen point to truncal muscle weakness and waddle to gluteal weakness. Weakness of the knees results in hyperextension of the knee, the genu recurvatum and high steppage gait points to foot drop. Patients with sensory ataxia have their eyes glued to the ground and a high steppage gait with foot dorsiflexed as the knee is bent, opposite of the foot drop.

1.1.3 Weakness

The most common symptom of neuromuscular diseases is weakness. It is important to ascertain what the patient means by weakness, as individuals use the word ‘weakness’ to describe a variety of phenomena ranging from loss of strength to sensory loss. The reverse is also true and patients who describe ‘numbness’ or ‘heaviness’ actually mean weakness. Inquiring into which actions and tasks are difficult to perform and how is the symptom affecting the patient’s daily life clarifies these issues. Often, from the history, it is possible to judge which muscle groups are weakened. This is an important step as diseases follow patterns in the way they affect muscle groups, leading to the anatomical and aetiological diagnosis. We shall now discuss some of the well-recognised patterns of weakness in neuromuscular disorders.

Weakness of the orbicularis oculi muscles manifests with inability to close eyes tight, soap entering eyes while washing face, redness of eyes, watering and later with exposure keratitis. Patients with slowly evolving bifacial weakness are unaware that their eyes remain open when asleep, and often relatives remark in the affirmative when this question is asked. In fact, this is a good question to ask the family members, when you suspect facioscapulohumeral dystrophy. Asymptomatic relatives often have this feature but do not realise that it is a mild and early manifestation of the same disease. Weakness of the orbicularis oris muscles results in inability to whistle, to blow and to suck liquids from a straw. Patients adjust to the very gradual development of the weakness and consider it to be ‘just the way I am’ and ‘I have never been good at it’ and may not mention the symptom to the doctor. The weakness of orbicularis oris muscle leads to downturning of lips, showing resemblance to ‘bouche de tapir’ appearance or the fish mouth. Bifacial weakness is

common in many conditions of the motor unit; it is more often neurogenic in origin, Guillain–Barré syndrome being the most likely diagnosis in clinical practice. Weakness of face can also be encountered in myasthenic patients and myopathies, e.g. facioscapulohumeral muscular dystrophy.

Drooping of the eyelids, blepharoptosis, is seen in a variety of neuromuscular disorders. It is fatigable and fluctuating in myasthenia gravis and congenital myasthenic syndromes and is often asymmetrical or unilateral in myasthenia gravis. Ptosis in myopathies is usually symmetrical and nonfluctuating. Myotonic muscular dystrophy, mitochondrial cytopathies, congenital myopathies and oculopharyngeal muscular dystrophy are associated with ptosis. On the neurogenic side, third nerve palsies are frequently encountered in clinical practice. The combination of ptosis and bifacial weakness is very suggestive of a myopathy or a disease of the myoneural junction.

Double vision accompanies ptosis in myasthenia, whereas it is conspicuously absent in most myopathies. As and when myopathies affect the external ocular muscles, the weakness is symmetrical and evolves gradually; hence diplopia does not occur. Myotonic disorders also produce external ophthalmoparesis. Some diseases like mitochondrial myopathies preferentially affect the external ocular muscles. Such patients have to turn their head while looking to a side, the head thrust. External ocular movements are also affected in some of the congenital myopathies and myasthenic syndromes. External ophthalmoplegia is an integral feature of Miller Fisher syndrome, botulism, some snake bites and various cranial neuropathies.

Weakness of the neck muscles presents with inability to hold the neck upright, and head may drop forwards or backwards, depending upon the dominant weakness. Some patients resort to supporting the jaw with hand to keep the neck erect or take to wearing a cervical collar for support. While getting up from supine position, head lag is noted. Patients experience neck pain while travelling in vehicles as the acceleration and deceleration cannot be tolerated by the weak neck muscles. Neck extensors or flexors may be preferentially weak in some diseases, but in most patients, both are affected. When the brunt of the disease is on the neck muscles, the diagnostic possibilities of inflammatory myopathies, motor neurone disease and myasthenia gravis should be considered. Nemaline myopathy, Pompe's disease and spinal muscular atrophies are the other diagnostic considerations. In the uncommon condition of isolated neck extensor myopathy, the weakness restricts largely to the single group of muscles. In conditions like GBS, the neck muscle weakness correlates with ventilatory insufficiency and hence is valuable. Diseases like myotonic muscular dystrophy preferentially affect the sternocleidomastoid muscles and result in the swan neck appearance. In myotonia congenita, on the other hand, the neck muscles may be hypertrophic. In patients with Hirayama disease, the length of the cervical segment may be longer when compared with length of the whole spine. The bearing of this observation on the pathophysiology of Hirayama disease is as yet unclear.

Muscles of respiration can be preferentially affected in neuropathies like Guillain–Barré syndrome and porphyria and in some myopathies like in acid maltase deficiency and nemaline myopathy; respiratory difficulties can also be related to

the changes in the skeleton like scoliosis, kyphosis and the development of contractures, resulting in incomplete lung expansion.

Difficulty in swallowing is encountered in myasthenia, motor neuron disease, spinal muscular atrophies, demyelinating neuropathies, diphtheritic neuropathy, oculopharyngeal muscular dystrophy and some mitochondrial myopathies. Effortless nasal regurgitation favours lower motor neuron dysfunction, while patients having upper motor neuron diseases tend to cough and choke on food. A note of this symptom should be taken as this has a bearing on the management and prognosis of patients. In myasthenia gravis, in addition to dysphagia, patients have difficulties in chewing. Painless chewing difficulty is very rarely seen beyond neuromuscular junction disorders. A proportion of patients suffering from giant cell arteritis have claudication pain, while chewing food and temporomandibular joint issues lead to pain and locking of jaw during mastication. In pseudobulbar palsy, as seen in motor neuron disease, emotionality accompanies dysphagia. In MuSK myasthenia and motor neurone disease, tongue is atrophic and weak, and patients are unable to roll food in their mouth, and food spills or cannot be pushed effectively. These patients also have dysarthria. Nasality to voice indicates weakness of the pharyngeal musculature and is seen in demyelinating neuropathies, myasthenia, botulism, etc.

Weakness of the shoulder girdle manifests with inability to raise arms above shoulder level, inability to take things down from high shelves and inability to comb and button clothes behind back. Examination shows the clavicular step (straightening of the clavicles) and anterior axillary fold, which is a result of the wasting of the pectoralis muscles. Weakness of the shoulder girdle is often associated with winging of the scapulae. Winging is seen in facioscapulohumeral muscular dystrophy, calpainopathy, dystrophinopathies, sarcoglycanopathies, brachial plexopathies, radiculopathies and injuries to the long thoracic nerve. Winging can be tested by many methods, pushing the wall being the most common; but bringing the arms down is perhaps the most effective. In the later method, the technique uses weight of the arms, unlike in pushing the wall. Trapezius weakness results in upper poles being separated, while the reverse is seen in serratus anterior weakness. The winging in FSHD is associated with riding of the scapula, and the overriding scapulae can be seen anteriorly as lumps in the trapezius muscles. Such riding is not generally seen in other diseases which result in winging of scapulae. Moreover, in FSHD, the scapular winging is often asymmetric in nature and visible at rest.

Weakness of the fingers and forearms manifests with inability to open lids, to perform precision tasks and to hold small objects. It is common with neurogenic conditions like motor neuron disease, carpal tunnel syndrome, cervical radiculopathies, lower brachial plexopathies, multifocal motor neuropathy, syringomyelia, etc. Some of the myopathies also affect these muscles, namely, myotonic muscular dystrophy, inclusion body myopathy, Welander myopathy and GNE myopathy. Except for myotonic dystrophy and to an extent inclusion body myopathy, the weakness and wasting tends to be symmetrical in myopathies. In facioscapulohumeral muscular dystrophy, the forearm musculature is well preserved, while the arm is wasted, the Popeye sign. Forearm flexors are preferentially affected in inclusion body

myopathy and forearm extensors in FSHD. In Hirayama disease, the brachioradialis muscle tends to be spared.

Trunk weakness presents with changes in stance and posture. Lordosis is perhaps the most common change, being seen in most myopathies and spinal muscular atrophies. This is the result of weakness of the paraspinal musculature. Scoliosis is seen in congenital myopathies, Duchenne muscular dystrophy, and is a part of inherited neuropathies, most pronounced in type CMT 4D. Extreme scoliosis can compromise the respiratory function. Kyphosis is uncommon in neuromuscular disorders but can be seen in any condition that affects the paravertebral musculature. Protuberant abdomen or visceroptosis is the result of weak abdominal muscles and lordosis. In some conditions like calpainopathies, the external oblique muscles may be so weak that herniae result. Unilateral abdominal herniae are seen in some patients having the uncommon diabetic truncal neuropathy. Lower segments of the rectus abdominis muscles may be weaker than the upper segments, resulting in Beevor's sign. This sign is consistently seen in patients with FSHD but has also been seen in other myopathies like GNE myopathy.

Hip girdle weakness is one of the most common presentations of neuromuscular disorders. Patients have difficulty in climbing stairs, rising from ground and rising from low chairs and sometimes find it difficult to turn in bed. Waddle is a much-discussed manifestation of the pelvic girdle weakness. Patients waddle when the gluteus medius is weak on both sides. As we know, gluteus medius originates from the iliac crest and inserts on the trochanter and helps to stabilise the pelvis when one leg is lifted off the ground. In the presence of weakness of this muscle, the anterior superior iliac spine drops as the leg is lifted, and when this alternates, waddle results. Waddle is common to many diseases of the muscle and nerves. Hip girdle weakness results in Gower's sign. This refers to the particular way in which patients rise from the ground, by gradually climbing on themselves, so to say. While it is most obvious in children having DMD, it is seen in a variety of neuromuscular conditions. In some patients with limb–girdle muscular dystrophies, the adductor muscles are weaker than the glutei. Such patients do not waddle but have a peculiar way of splaying their thighs as they rise from the ground. This hip abduction sign is seen in limb–girdle muscular dystrophies which have adductor weakness, for example, calpainopathies. Patients with Pompe's disease are known to turn prone, flex the hip and knee on one side and then use it as a lever to rise from the ground. Demyelinating neuropathies can have profound proximal weakness and result in waddle and Gower's sign.

Foot drop can be a presenting or a prominent feature of neuropathies, radiculopathies, anterior horn cell diseases and some myopathies. While it is generally symmetrical in myopathies and inherited neuropathies, asymmetry is seen in diseases of the anterior horn cells and roots. As foot drop develops, gait assumes high steppage and is easily noticed by onlookers. Toes do not clear the ground well and hence patients tend to fall on uneven surfaces. Bilateral foot drop develops in the course of inherited neuropathies and is an integral part of most neuropathic processes that have a motor component. Pressure palsies at the head of the fibula commonly result in unilateral foot drop in clinical practice. Amongst myopathies, GNE myopathy presents with severe foot drop in the initial stages when they are otherwise strong.

In an occasional patient with dysferlinopathy, the brunt of the weakness is on the tibialis anterior muscle, the distal myopathy with anterior tibial weakness (DMAT) phenotype.

Weakness of the gastrocnemius muscles results in inability to stand on toes and is appreciated during sporting activities, dancing, etc. It is an early feature of Miyoshi myopathy and anoctaminopathies.

Asking the patient to walk normally, walk on heels and toes, rise from a chair or ground, lift arms overhead and close eyes can give very important early inputs into the areas of further analysis.

1.1.4 Cramps, Pains, Fatigue and Exertional Symptoms

Cramps and muscle pains are common. Cramp refers to a painful knotting up of muscles, usually affecting calf muscles. These are seen in endocrine diseases like hypothyroidism, electrolyte disturbances, renal diseases and metabolic myopathies like McArdle disease. In a large proportion of patients, the precise mechanism cannot be deciphered. Diffuse aches and pains are also very common and are known to be the presenting symptom of osteomalacic myopathies. These are also associated with rheumatological conditions like polymyalgia rheumatica. When these symptoms are not associated with weakness, the diagnostic yield is less. Fatigue is more often a manifestation of systemic diseases like anaemia and hepatic or renal dysfunctions. Most individuals refer to fatigue in a general way, meaning thereby difficulty and tiredness in performing activities. Fatigability of neuromuscular disorders is distinct, as it tends to involve selected groups of muscles like eyelids, external ocular movements, chewing, swallowing, neck extension, etc. and exhibit diurnal fluctuation with intermittent normalcy. The difference between weakness and fatigue is the first contraction, which is strong in the latter. Exercise-related exacerbations of symptoms are common with metabolic myopathies, storage diseases and periodic paralysis, but it is important to remember that almost all sufferers of weakness will experience some increase of difficulty and sense of fatigue when exercising affected muscles.

1.1.5 Hypertrophy and Atrophy

Hypertrophy of the muscles is an important clinical sign. Severe hypertrophy favours muscle diseases. Duchenne and Becker muscular dystrophies are probably the most common muscle diseases where hypertrophy is pronounced. While it manifests in the calf muscles, glutei, deltoids, brachioradialis and masseter muscles may be enlarged. Milder degrees of hypertrophy may also be seen in sarcoglycanopathies, LGMD 2I and other LGMDs as well. Individuals having myotonia congenita have very well-developed musculature and herculean appearance. Hypothyroidism can present at times with enlargement of muscles (Hoffman and Kocher–Debre–Semelaigne syndromes) and, rarely, infestation of muscles by cysticercosis;

trichinosis has also been known to enlarge muscles. In cases of cysticercosis, asking the patient to stand on toes will reveal multiple knots (cysts) within the bulk of calves. Mild hypertrophy is seen in diseases of the anterior horn cells (spinal muscular atrophy), radiculopathies, neuropathies and many forms of myopathies.

Atrophy is common with neurogenic conditions in general, but as the disease course becomes chronic and weakness increases, myopathic muscles also become atrophic. Within the neurogenic causes, atrophy is most prominent with anterior horn cell diseases and axonal neuropathies. In contrast, demyelinating neuropathies show well-maintained muscle bulk in face of profound weakness. However, with chronicity, this distinction gets blurred.

1.1.6 Myotonia

Delayed relaxation after sustained contraction, the myotonia, is a very useful clinical feature. Patients may complain of generalised stiffness or slowness of activities. Some realise that they cannot let go, after holding things in their hands. Symptoms generally increase in cold. In most myotonias, exercise improves the movements. Patients learn that if they start moving their limbs before an anticipated movement, they perform better. A patient reported that he would get up and start movements of legs, few minutes before his local train station arrived, so that he could get off easily. In paramyotonia congenita, von Eulenburg disease, activity worsens symptoms, as does cold temperature. Paramyotonia affects upper body more prominently, e.g. eyelid myotonia. Weakness accompanies myotonia in myotonic dystrophy, whereas it is minimal, if present, in myotonia congenita. Myotonic dystrophy, as mentioned earlier, has multisystem manifestations. Myotonia is examined by asking the patient to grip for 10–15 s and then observing the relaxation process, the grip myotonia. It can also be assessed by percussing with a pointed hammer, the percussion myotonia. Usually, both methods elicit myotonia. In neuromyotonia, which is a result of peripheral nerve hyperexcitability, patients have posturing at rest and may have sensory symptoms; grip myotonia is demonstrated but percussion myotonia is usually absent.

1.1.7 Sensory Features

The distribution and type of sensory symptoms can help clinical localisation. Burning paresthesias are common in small fibre neuropathies, while heaviness and numbness suggest larger fibre involvement. Outstanding sensory changes with sparing of the motor system and deficits reaching the trunk area favour neuronopathies. Focusing on the early events is important as advanced mononeuritis multiplex can simulate a polyneuropathy. Sensory examination requires cooperation from the patient and hence is inherently subjective. When the examiner judges that sensory examination is vital to his diagnostic process, it may be useful to test the sensations first, when the patient is fresh and obliging. Touch is tested with cotton wool or examiner's finger, pain by a sharp pin and vibration by a set of tuning forks. Normal side could be tested

first so that patient familiarises with the testing process. As the appearance of sensations is easier to detect than others, examiner can start with the abnormal area and work towards normal, instructing the patient to report various perceived changes. The aim of the sensory examination in the context of neuromuscular disease is to establish a pattern of sensory loss. Mononeuropathies and radiculopathies will result in sensory findings in the area of the affected nerve or root. The initial documentation also helps tracking progress. While dealing with generalised neuropathies, a glove and stocking pattern is noted. It is important to appreciate the symmetric, distal to proximal graded nature of such sensory deficits, as they point to a length-dependent process. It is also important to study the proximal levels of the glove or stocking. In truly length-dependent diseases, the proximal deficits are almost in a circumferential manner. On the other hand, when multiple radicles are affected in addition to nerves, like seen in chronic inflammatory demyelinating neuropathies, the proximal margins of the deficits will be variable, pointing to the root involvement. In a minority of patients with demyelinating neuropathies, a delay between application and perception of the stimulus can be clinically appreciable. Patients having sensory ataxia show pseudo-athetoid 222movements of the outstretched hands and Romberg's test is positive. Particular care needs to be exercised in interpreting the findings of muscle power testing in such patients as sensory cues are missing and looking at the action being performed (visual cues) can improve the application.

1.1.8 Tendon Reflexes

Tendon reflexes reflect the integrity of the reflex arc and hence are diminished or are absent in neurogenic diseases. Changes in the deep tendon reflexes are most marked when the sensory system is affected and areflexia is most common with neuropathies affecting sensations. When only the motor system is affected, e.g. spinal muscular atrophy, reflex changes correlate with the degree of weakness in the affected segments. It is widely held belief that deep tendon reflexes tend to be well preserved till late in myopathies. However, reflex changes can be seen early as well. For example, knee jerk and upper limb reflexes can be diminished or absent early in DMD, even in young patients having mild weakness. This is believed to be due to the intrafusal muscle fibre disease, and, indeed, dystrophin has been shown to be deficient in the muscle spindles. The ankle reflex tends to be well elicited in most myopathies, unlike neuropathies. In Lambert–Eaton myasthenic syndrome, deep tendon reflexes may be absent or diminished at rest and are better elicited after exercise.

1.2 Differentiating Anterior Horn Cell Diseases from Myopathies

While it is somewhat easy to localise sensorimotor deficits to anatomical substrates, it can be difficult to differentiate the two pure motor localisations, anterior horn cells and muscle. Myopathies are largely symmetrical and proximal in nature, while

anterior horn cell diseases tend to be asymmetrical and involve the proximal as well as distal segments. Wasting is more prominent than weakness in anterior horn cell diseases, while muscle bulk is maintained or increased in weakened musculature. Very prominent hypertrophy is not encountered beyond myopathies. Fasciculations often accompany wasting and weakness and point to anterior horn cell diseases. While fasciculations clinically link strongly with anterior horn cell diseases, their electrophysiological origin is in the distal nerve segment, and hence they can be seen in many diseases of the lower motor neuron, e.g. radiculopathies and neuropathies. Hyperthyroid myopathy patients can manifest movements like fasciculations. Deep tendon reflexes tend to be lost in proportion to weakness in anterior horn cell diseases, while they may be well preserved in myopathies. This is particularly true for the ankle reflex, as mentioned earlier. Fasciculations point to neurogenic conditions, while an occasional thyrotoxic myopathy can do the same. Tremulousness and polyminimyoclonus of upper limbs are seen in neurogenic diseases. Myopathies follow a pattern of weakness depending upon the disease in question, while anterior horn cell diseases are rather featureless in distribution.

While these guidelines are important, it should be realised that all these are broad generalisations and exceptions are not uncommon. For example, distal myopathies are well known, inclusion body myopathies show prominent wasting, FSHDs are almost always asymmetrical, thyrotoxic myopathies fasciculate, knee and supinator reflex may be absent in ambulatory DMD patients, and muscle hypertrophy is seen in SMAs. Thus, the clinical process of differentiation between myopathies and anterior horn cell diseases can be challenging. Moreover, it is possible that the dysfunctions of the lower motor neuron are interlinked in ways that we have not deciphered. At which level of the organisation of the lower motor neuron are patterns of muscular weakness determined is unclear. For example, hip adductor group of muscles are much weaker than abductors in limb–girdle dystrophies. Does this link to mechanistic factors or neural organisation? Lastly, it is important to appreciate that the lower motor neuron functions as a single unit, and hence, in chronic diseases, clinical differentiation can get indistinct.

1.3 General Examination

Clues to the neuromuscular diagnosis can be obtained from general examination. The skeleton is affected in a variety of diseases. Pes cavus and kyphoscoliosis point to inherited neuropathies. It is important to study the pes cavus in weight bearing and non-weight-bearing positions. Intrinsic foot muscle weakness and wasting gives the appearance of pes cavus, which flattens out as patients stand. Bony pes cavus does not change on standing and light can be seen passing through both arches of feet. Short stature points to mitochondrial disorders and may also be seen with early onset of neuromuscular diseases. Facial dysmorphisms are seen in inherited conditions. Skin examination can be helpful. Rashes point to immune-mediated disorders like dermatomyositis or systemic lupus erythematosus. Skin pigmentation can be associated with deficiency states like B12 deficiency or with adrenal failure

as seen in adrenomyeloneuropathy. Hyperkeratosis of palms and soles is encountered in toxic neuropathies, e.g. arsenic toxicity, and nails in such patients show Mee's lines. Thallium toxicity is associated with loss of hair and mercury poisoning leads to acrodynia. Patients with autonomic neuropathy lose hair on the distal parts of limbs, and conditions like Fabry's disease and cerebrotendinous xanthomatosis can be diagnosed by the characteristic angiokeratomas and accumulation of lipids under the skin, respectively. Joints may be involved in immunological disorders which associate with inflammatory neuropathies or myopathies and can be the presenting features of a neuromuscular disease, e.g. arthrogryposis and congenital dislocation of hips. Hyperelasticity of the distal joints is seen in collagenopathies like Ullrich disease, combined with contractures of proximal joints. Bethlem myopathy sufferers have keloids in addition to contractures and myopathy. Early contractures in general point to involvement of the collagen system. In eosinophilic fasciitis, the subcutaneous tissues get thickened and 'wood-like'. Deafness and retinitis pigmentosa are seen in mitochondriopathies. Retinal telangiectasias are seen in some patients with FSHD, the Coats' disease. Hepatosplenomegaly may be seen in metabolic myopathies. Cardiomyopathies and cardiac arrhythmias are seen in many neuromuscular conditions: dystrophinopathies, sarcoglycanopathies, autosomal dominant LGMDs, myotonic dystrophies and Andersen–Tawil syndrome, to name a few. Thus, a good general and systemic examination can provide valuable information.

1.4 Concluding Remarks

As can be seen from the above discussion, a sound clinical approach based on detailed evaluation of the patient's symptoms, in depth review of the family history and paying attention to pattern recognition can lead the clinician to arrive at a working set of differential diagnosis which can then be fine-tuned with the help of investigations. In the current era of availability of tests, in particular, the genetic tests, Pandora's box has only recently been opened. Many phenotypes of a gene and many genotypes of a phenotype are commonplace. The marriage of clinical and genetic information will evolve with time. However, as patients, and not the gene chips, will continue to walk into our consulting rooms, clinical base will never go out of fashion.

1.5 Organisation of This Book

This book has been divided into eight parts, based on the clinical presentations, e.g. predominantly motor diseases, predominantly sensory diseases, symmetric and asymmetric diseases, etc. This approach has been adopted, keeping the clinician in mind. Some diseases can present symmetrically or asymmetrically; these have been included in one of the two categories (e.g. acute motor axonal neuropathies, facioscapulohumeral muscular dystrophy), and the reader is urged to put this aspect in context.

Three categories of chapters have been created: chapters that deal with a single disease entity (e.g. acute motor axonal neuropathy), those that cover a small group of conditions (e.g. Hirayama disease and other focal amyotrophies) and those that encompass a large group of conditions (e.g. limb–girdle muscular dystrophies). Each chapter has been formatted under the conventional headings of introduction, epidemiology, clinical features, investigations, differential diagnosis, management and prognosis, followed by references. For the ease of reading and assimilation, a table-based approach has been adopted throughout the book. Thus, the clinical features, investigations, differential diagnosis and management issues have been organised as tables. The information in the tables appears as points, which have been well referenced for the interested reader to build further. Many chapters carry case studies. The cases presented at the end of the chapters make important points which put in perspective the information provided in the foregoing chapters. Some cases deal with issues which have not been included in the text of the chapters and thus complement the chapters. Each chapter ends with boxed key points which could be used as revision and for quick reference.

Part I

Asymmetric Motor Weakness

Motor Neuron Diseases (Amyotrophic Lateral Sclerosis)

2

2.1 Introduction

ALS, PMA (progressive muscular atrophy) and PLS (primary lateral sclerosis) are common MNDs. Charles Bell gave early descriptions of this heterogeneous group of neurodegenerative disorders in 1830. Most cases are sporadic and exhibit a combination of upper and lower motor neurone features, often in the same segments. Familial incidence of ALS was described in scattered publications beginning in the mid-1800s but received limited attention in the literature until the report in 1955 by Kurland and Mulder, which suggested that ALS may be familial in nearly 10% of cases (Kurland and Mulder 1955a, b). Common inheritance pattern of familial ALS is autosomal dominant; rarely it can be autosomal recessive or X-linked dominant. ALS is genetically heterogeneous with over 50 potential causative or disease-modifying genes identified, but C9ORF72, SOD1, TARDPB and FUS presently account for over 50% of ALS-linked gene variants found in ALS patients, and variants in other genes are relatively uncommon or rare (Boylan 2015).

2.2 Epidemiology

The incidence is 1.5–2/100,000/year, the prevalence 3–8 per 100,000 and the mortality 1.9/100,000/year (Kahana et al. 1976; Logroscino et al. 2005). Early-onset ALS is commonly seen in males. Sporadic cases are common. Only 5–10% cases are familial. Older age, male sex and genetic structure are proven risk factors for ALS. Environmental factors may act by producing oxidative stress, for example, smoking. Possible risk factors are physical activity, exposure to heavy metals like lead, head injury, electromagnetic fields and farming chemicals (Oskarsson et al. 2015).

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2.3 Clinical Features

2.3.1 Symptoms of ALS

Age of onset is commonly in fifth or sixth decades; infrequently it is known to begin at early age, as early as second decade of life. A plethora of symptoms is known to be associated with ALS. Symptoms and signs of ALS have been summarised in Tables 2.1 and 2.2.

Table 2.1 Symptoms of ALS

1.	Weakness	Weakness presents first in the limbs, the spinal onset ALS or the bulbar regions In the limbs, this occurs in an asymmetrical distal pattern, as a claw hand or foot drop. The progression of ALS classically follows a segmental pattern, for example, first starting in the left arm, then left leg, then right arm, then right leg. There is no predictor of the time of involvement for each limb. Periods of symptomatic stabilisation may occur. Early bulbar dysfunction occurs particularly in older females with slow spastic dysarthria, dysphagia and pseudobulbar affect. The areas of weakness that are relatively specific for ALS include thoracic paraspinals, posterior neck, tongue, jaw, first dorsal interosseous and tibialis anterior muscles. ALS rarely, if ever, presents with fasciculations without weakness (Eisen and Stewart 1993)
2.	Pain	Two thirds of patients Described as burning, aching, cramping and shock-like Occurs at all stages of the illness Does not necessarily correlate with depression Associated with increased disability. Common causes of pain are felt to be related to limited range of motion in joints, general immobility, spasticity and/or cramps (Pizziementi et al. 2013; Chio et al. 2012; Pagnini et al. 2012; Newrick and Langton-Hewer 1985)
3.	Cramps	Commonly affect the legs at night May be severe in the early stages but often resolve spontaneously with disease progression (Eisen and Stewart 1993)
4.	Fatigue	Multifactorial with sleep disruption, nocturnal complaints such as nocturia and cramps, nutritional depletion, weakness, vital capacity, functional status, depression and medications including riluzole all potentially playing a role (Ramirez et al. 2008)
5.	Weight loss and nutrition	Cause: Dysphagia, muscle atrophy, poor appetite related to depression and hypermetabolic state (Mascaritioli et al. 2012; Desport et al. 2001; Dupuis et al. 2011). In addition, caloric needs in an ALS patient may be amplified because of increased work of using weak muscles, cramps, spasticity, fasciculations and pseudobulbar manifestations An accurate way to measure an ALS patient's total daily caloric needs uses the Harris–Benedict equation (Kasarskis et al. 2014)
6.	Sialorrhoea	Socially embarrassing symptom Related to pharyngeal muscle weakness Increase risk to aspiration pneumonia (McCullagh et al. 1999)

Table 2.1 (continued)

7.	Emotional lability	Involuntary emotional outbursts with or without provocation, which is irrelevant to situation (McCullagh et al. 1999)
8.	Sleep disruption	It can be physical (weak respiratory muscles or pain) or psychological (Arnulf et al. 2000)
9.	Breathlessness	Respiratory failure may occur in isolation Hence it is important to check for neck weakness and routinely ask about orthopnoea. The accessory muscles of respiration become flaccid over time Morning headache may be an early symptom of hypoventilation Interestingly, respiratory failure can be associated with loss of taste, weight loss and depression
10.	Laryngospasm	Laryngospasm is caused by sudden and strong contraction of adductors of larynx. Patient feels chocking sensation. It may be associated with inspiratory stridor or audible respirations. Common causes of laryngospasm in ALS are liquid or saliva in contact with the larynx, acid reflux, smoke, strong smells, emotion, alcohol, cold bursts of air and even spicy foods
11.	Jaw involvement	Jaw quivering or clenching due to spasticity, precipitated by pain, anxiety or cold Jaw clenching can be severe enough to interfere with oral hygiene
12.	Oedema	Usually in dependent portion due to immobility and change in muscle pump function
13.	Uncommon symptoms	Occasional sensory symptoms, frontal lobe cognitive dysfunctions (Lomen-Hoerth et al. 2002), Spastic bladder, dysautonomia and extraocular muscle involvements are uncommonly encountered

Table 2.2 Clinical signs in ALS

LMN involvement	Weakness, muscle atrophy and fasciculations indicate LMN involvement. Tongue atrophy is a useful clinical sign (Fig. 2.1). Split hand syndrome or dissociated hand muscle atrophy (relative wasting of APB and FDI muscles with sparing of ADM muscle) (Fig. 2.2) (Kuwabara et al. 2008)
UMN involvement	1. Brisk reflexes 2. Hypertonia 3. Extensor plantar response is less common UMN signs are inconsistent as normal physiological release functions are affected by motor neurons degeneration

Juvenile ALS is one which starts at the early age, i.e. younger than 25 years. It progresses slowly as compared to other forms of ALS (Sabatelli et al. 2008).

2.3.2 Clinical Signs in ALS

Weakness, wasting, fasciculations, brisk reflexes and hypertonia are common examination findings. (Table 2.2).

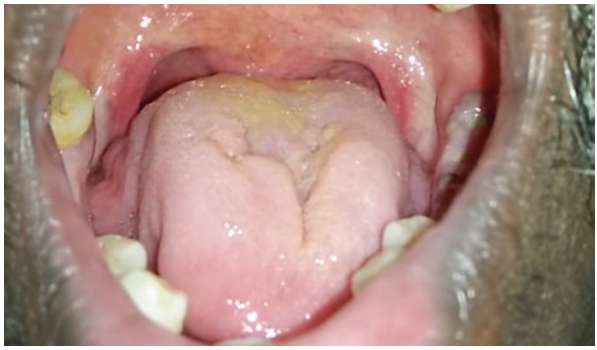

Fig. 2.1 Tongue atrophy in a patient with ALS

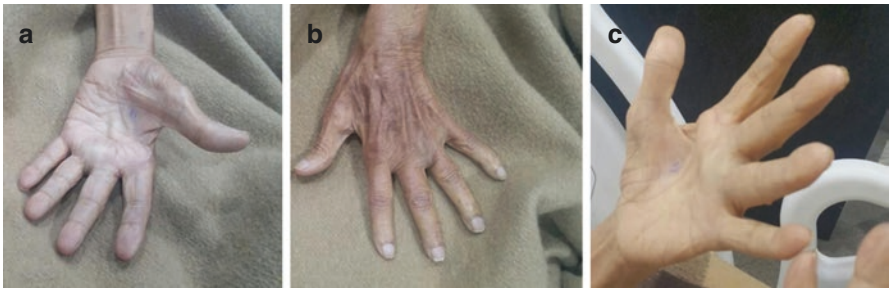

Fig. 2.2 Dissociated (split) hand (**a**) wasted thenar eminence, (**b**) wasted FDI and (**c**) well-maintained ADM in a patient with ALS

2.3.3 Regional Variants of ALS

Regional ALS variants have symptoms isolated to a single spinal cord region for periods of time longer than 1 year. Regional ALS variants may have slower disease progression so are important clinical distinctions (Jawdat et al. 2015). Regional variants of ALS include brachial amyotrophic diplegia, leg amyotrophic diplegia, dropped head syndrome, isolated bulbar ALS and respiratory onset ALS (Table 2.3).

2.3.4 Clinical Spectrum of MND

2.3.4.1 PMA and PLS

As can be seen from the above discussion, the clinical spectrum ranges from pure lower motor neurone to pure upper motor neuron findings, and there are associated features of other system involvements. These are depicted in Fig. 2.3. ALS variant may have isolated UMN involvement (known as PMA) or isolated LMN involvement (known as PLS) (Fig. 2.3) (Younger et al. 1988). Asymmetry of UMN signs can be persistent for a long time in ALS (Gordon et al. 2009). Please refer to chapter on PMA for its details.

Table 2.3 Regional variants of ALS

Flail arm syndrome (Vulpian–Bernhardt syndrome), scapulohumeral form of ALS, neurogenic man-in-a-barrel syndrome, hanging arm syndrome, brachial amyotrophic diplegia	Male predominance Restricted involvement of upper limbs lasting for at least 12 months Lower limbs: Normal or abnormal reflex or abnormal tone Usually progress to generalised form Better prognosis than generalised form
Flail leg peroneal form of ALS, pseudopolyneuritic (Marie–Patrikios form)	Restricted involvement of lower limbs for at least 12 months Upper limbs: Subtle UMN sign may be present Later progresses to generalised form
Dropped head syndrome	Rare Restricted to neck extensors
Bulbar onset ALS	Patients with bulbar onset ALS have worst prognosis amongst all regional variants of ALS
Respiratory onset ALS	Restricted to respiratory muscles Male are commonly affected Presentation: Orthopnoea, dyspnoea Poor prognosis
Hemiplegic variant of ALS Progressive hemiplegia Mills syndrome	Unilateral progressive UMN signs on one side of body Later involves unaffected side

Wijesekera et al. (2009); Gourie-Devi et al. (2003); Rajabally et al. (2005); Shoesmith et al. (2007)

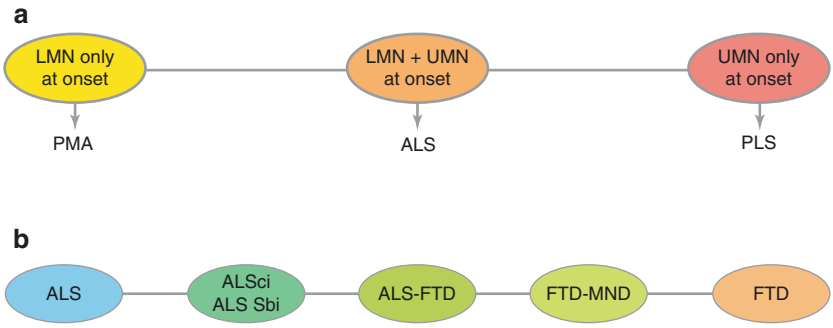

Fig. 2.3 Spectrum of motor neuron diseases. *ALS-Sci* ALS cognitive impairment; *ALS Sbi* behavioural impairment

2.3.4.2 ALS and Dementia

Frontal cognitive and motor dysfunction observed in ALS are as follows (Achi and Rudnicki 2012; Donaghy et al. 2011):

- Behaviour variant of FTD
- Apathy
- Disinhibition
- Delusion
- Stereotypy
- Depression
- Eye movement abnormality

2.3.4.3 ALS with Multisystem Involvement

Observations from patients who survived long have suggested that ALS can affect eye movements, autonomic function and sensory system later on (Atsuta et al. 2009). As Table 2.4 shows, the following patterns of multisystem involvement are known in association with ALS.

A variety of genes are known to be associated with ALS, and Table 2.5 describes their salient clinical feature and genes linked to ALS pathogenesis (Boylan 2015; Leblond et al. 2014; Su et al. 2014; Renton et al. 2014; Marangi and Traynor 2014).

Table 2.4 ALS with multisystem involvement

Clinical syndrome	Key features
ALS and extrapyramidal features	
ALS–Parkinson dementia syndromes of Guam (Steele and McGeer 2008)	
Kii Peninsula (Kokubo 2015)	
ALS–PD complex/Brait–Fahn–Schwartz syndrome (Gilbert et al. 2010)	1. Typical PD 2. Good response to dopamine 3. Simultaneous or later involvement of motor neurons
PD–ALS–FTD syndrome	PARK 7 (DJI) mutation
ALS–parkinsonism (Park et al. 2011)	Levodopa nonresponsive Nigrostriatal degeneration
Chorea and/or hemiballismus (Cooper-Knock et al. 2013)	C9orf72 mutation Late onset HD and ALS
ALS and cerebellar ataxia (Van Damme et al. 2011)	C9orf72 mutation, SCA 2 – ATXN2 mutation
ALS and sensory involvement (Isaacs et al. 2007)	Subjective sensory symptoms (50%) Objective sensory signs (10%) Sensory ganglionopathy (rare) Commonly seen with SOD1 (D90A) mutation
ALS with urinary and autonomic involvement	C9orf72 mutation
Andersen and Al-Chalabi (2011)	SOD1 (Asp90Ala) mutations
ALS with deafness (Bandettini Di Poggio et al. 2014; Nalini et al. 2013)	Brown–Vialetto–Van Laere syndrome, Madras motor neuron disease

Table 2.5 Gene loci and clinical hallmarks of familial ALS

Clinical hallmarks	Genetic loci
Dementia and or parkinsonism	VEGF-linked ALS (VEGF; 6p21.1) FTD-ALS type 2 (CHCHD10; 22q11.23) associated with sensorineural hearing loss, ataxia and myopathy ALS–parkinsonism/dementia complex type 1 (TRPM7; 15q21.2) DCTN1-linked ALS (DCTN1; 2p13.1) NEFH-linked ALS (NEFH; 22q12.2) Juvenile ALS with dementia
Severe dysphagia	NEFH-linked ALS (NEFH; 22q12.2)
Vocal cord palsy	DCTN1-linked ALS (DCTN1; 2p13.1)
Paget's disease of bone	SQSTM1-linked ALS (SQSTM1; 5q35.3)
Ptosis and gynaecomastia	Utah juvenile ALS cluster

2.3.5 Diagnosis of ALS

The clinical diagnosis of ALS is often evaluated by using the revised El Escorial criteria, which were developed for clinical trials but are widely used in clinics (Brooks et al. 2000).
Clinically definite: UMN + LMN signs

- In bulbar region +2 spinal cord level or
- In 3 spinal cord level

Clinically probable:

- UMN + LMN signs in 2 spinal cord level and
- UMN signs rostral to LMN signs

Clinically probable – laboratory supported:

- UMN + LMN signs in 1 spinal level or
- UMN signs in 1 spinal level + LMN signs in 2 spinal level on EMG

Clinically possible:

- UMN + LMN in 1 spinal level or
- UMN in 2 spinal level or
- LMN rostral to UMN

Clinical features in general do not reliably separate familial from sporadic ALS in individual patients (Boylan 2015).

2.4 Pathophysiology

ALS is a clinical syndrome named for its neuropathological hallmark, loss of motor neuron in cortex, spinal anterior horn cells and lateral spinal column axons. The neuropathological molecular defect is the TDP-43 immunoreactive neuronal cytoplasmic inclusions. These inclusions are seen in the sporadic as well as most of the familial cases (Saberi et al. 2015).

Genetic, environmental and epigenetic factors are involved in ALS pathogenesis. Epigenetic factors are DNA methylation, histone remodelling, RNA editing and micro-RNA modifications (Paez-Colasante et al. 2015) Cognitive decline in ALS is attributed to atrophy of layer five of the frontotemporal lobe (Achi and Rudnicki 2012).

2.5 Investigations

Investigations are directed to confirming the widespread nature of the anterior horn cell involvement ant at ruling out the differential diagnosis (Table 2.6).

2.5.1 Electrodiagnosis

Electrodiagnostic testing is very important and needs to be performed by well-trained experts and with great thoroughness. If only LMN signs are present on initial examination, an EMG/NCS is mandatory to exclude other possibilities, such as

Table 2.6 Investigations in patients with ALS

All patients	Complete blood count, erythrocyte sedimentation rate, random blood sugar, renal function tests, liver function tests, electrolytes thyroid function, B12, ANA, rheumatoid factor, serum protein immunofixation and electrophoresis, CK levels and intact parathyroid hormone (iPTH)
All patients	Electrodiagnosis
Most patients	Brain and/or cervical spine MRI (depending on clinical syndrome) with gadolinium enhancement
Rarely	Nerve–muscle biopsy, CSF analysis
Patients younger than 40 years	Hexosaminidase A levels for adult-onset Tay–Sachs disease
Early bowel/bladder involvement	Consider HTLV-1 testing
Possible toxic exposure	Urine heavy metal screening panel
If family history of ALS	Genetic testing screening for malignancy (lymphoma, lung cancer)

Table 2.7 Electrodiagnostic checklist for ALS (Baek and Desai 2007) (Table 2.4)

Normal sensory responses
No conduction block in the motor responses at non-compressible sites exclude Martin Gruber anastomosis if conduction block is present in the upper limb
Test three muscles each, proximally and distally, in at least two limbs
Test thoracic paraspinal or genioglossus
EMG shows areas with combination of acute denervation and chronic reinnervation
Florid spontaneous activity
UMN signs on examination in same areas
Evidence of acute denervation in clinically uninvolved areas

multifocal motor neuropathy with conduction block, spinal muscular atrophy, myopathies, polyradiculopathy/plexopathy and neuromuscular transmission disorders; to delineate widespread clinical and subclinical involvement in myotomes; and to confirm the combination of active denervation and reinnervation, which is the hallmark of ALS.

Nerve conduction study should involve upper limb nerves (median, ulnar) and lower limb nerves (sural, peroneal) Carefully search for signs of demyelination like conduction block and/or conduction block or sensory abnormalities. EMG should be performed in at least two limbs and three muscles each, proximally and distally, looking for the combination of acute denervation with florid fibrillation potentials and positive sharp waves, and very large amplitude motor units with markedly decreased recruitment which are the electrodiagnostic signature of ALS. Fasciculations that are missed on clinical examination are occasionally detected electrophysiologically. EMG of the thoracic paraspinal muscles should be routinely performed to look for spontaneous activity; lumbar paraspinals are not helpful in differentiating between ALS and a lumbosacral polyradiculopathy. In early cases where there is no tongue atrophy, needle examination of the genioglossus, revealing fibrillation potentials and positive sharp waves, can be very helpful in establishing the cause of a diffuse LMN process. This is especially helpful in situations where there is a concomitant cervical spondylotic myelopathy complicating the analysis of the extremity abnormalities. Following points can help in electrodiagnosis of ALS (Table 2.7).

2.5.2 Pulmonary Function

Patients with ALS should have an assessment of pulmonary function every 3–6 months. Forced vital capacity (FVC) is used for evaluation and prognosis of respiratory function (Czaplinski et al. 2006). In most cases, however, the earliest detectable abnormality is a reduction in maximum inspiratory pressure, sniff nasal pressure, sniff transdiaphragmatic pressure or nocturnal oximetry (desaturations <90% for one cumulative minute) (Jackson et al. 2001). Supine FVC is superior to standing FVC for prognosis (Lechtzin et al. 2002).

2.5.3 Secondary ALS

As ALS-like presentation is known to occur in association with or secondary to paraproteins, hyperparathyroidism, heavy metal toxicity and occult or overt neoplasms, these should be carefully excluded with the help of relevant investigations as outlined in Table 2.6.

2.6 Differential Diagnosis

Following groups of diseases are considered in the differential diagnosis. Given the stark prognosis of ALS, it is extremely important not to overlook any modifiable condition (Table 2.8).

Table 2.8 Differential diagnosis

Diagnostic category	Key differentiating features
Other motor neuron diseases	
Spinobulbar muscular atrophy or Kennedy disease (Grunseich and Fischbeck 2015) Spinal muscular atrophy (SMA)	X linked Onset in fourth or fifth decade Slow progression Trinucleotide repeat disorder (CAG) Responsible gene is androgen receptor gene Associated with infertility, gynaecomastia Only LMN signs, younger age of onset and positive family history favour SMA
Structural diseases	
Cervical spondylotic myelopathy, Arnold–Chiari malformation, syringomyelia/bulbia, CNS irradiation and tumour, stroke	Spinal cord, roots and cranial nerve involvement in combinations, dissociated sensory loss and sphincter involvement
Immune/inflammatory	
MMNCB	The relative preservation of muscle bulk, weakness in named peripheral nerve distributions and upper extremity involvement with very slow progression of weakness and relative lack of active denervation on EMG are usually the tips for considering the diagnosis
CIDP Multiple sclerosis Myasthenia gravis Inclusion body myositis	Sensorimotor neuropathy, no UMN features UMN features alone, brainstem and spinal cord syndromes Ptosis, diplopia, chewing and swallowing difficulty, fatigability Pure motor, asymmetric LMN syndrome with brunt on forearm flexors and quadriceps muscles
Infections	
HTLV 1 myelopathy or tropical spastic paraparesis	Onset: Fourth decade Symptoms: Lower limbs pain and paresthesias, bladder problems Signs: UMN signs more prominent than LMN signs Diagnosis: Serology or PCR from blood or CSF

Table 2.8 (continued)

Diagnostic category	Key differentiating features
HIV	Myelopathy, neuropathy
Metabolic	
Adrenomyeloneuropathy	Slow progressive spastic paraparesis Peripheral neuropathy Bowel/bladder may be involved Associated adrenal insufficiency Diagnosis: VLCFA levels in plasma, RBCs or cultured skin fibroblasts
Hyperparathyroidism	Asymmetric muscle weakness, atrophy, hyperreflexia without spasticity and Babinski sign
Toxic	
Lathyrism	Regular use of flour made from *Lathyrus sativus* (chickling pea) Acute to chronic onset Muscle pain, cramps, spasms, weakness Bladder symptoms Sensorimotor spastic paraparesis Rarely coarse tremor in upper limbs
Post-polio syndrome/progressive postpoliomyelitis muscular atrophy (PPMA)	History of polio Period of stability for minimum 10–15 years Diagnosis of exclusion Progressive focal asymmetric weakness
Hereditary	
Adult Hex-A deficiency	Autosomal recessive disorder Onset: Second decade Progression: Slow Proximal muscle weakness Cramps Dysarthria Spasticity Sensory involvement Cognitive decline Psychiatric manifestation Extrapyramidal feature Cerebellum involvement EMG suggestive of complex repetitive discharges as well as abnormal sensory potentials
Four-A syndrome (Allgrove syndrome)	Autosomal recessive Achalasia Alacrimia Adrenocorticotrophic insufficiency Amyotrophy
Adult polyglucosan body disease	Adult onset Slow progression UMN + LMN signs Cognitive impairment Sensory neuropathy Bowel/bladder involvement Tissue diagnosis shows PAS-positive polyglucosan bodies in cytoplasmic location

2.7 Management

2.7.1 Molecules: Approved and in Development

Riluzole is approved molecule for ALS management which has property of anti-glutamate toxicity. It prolongs the median survival by 2–3 months due to its ability to delay respiratory dysfunction. It has no role in motor symptoms, tremulousness and FVC changes (Bensimon et al. 1994; Deng et al. 2009) and is of less benefit to older and severely affected patients (Borras-Blasco et al. 1998). The main side effects of riluzole therapy are gastrointestinal upset, but it can cause elevation in liver transaminases. When starting riluzole therapy, it is recommended to check liver profile at baseline, then 1 month after starting therapy and then every 3 months for the first year. In May 2017, edaravone has also found a place in the therapy of ALS.

Figure 2.4 shows drugs under research for ALS and its relevant molecular pathways (Moujalled and White 2016).

2.7.2 Gene Therapy Efforts

Common ALS pathology is RNA or protein-mediated toxic gain of function. Gene therapy by modification of these paths is aimed at reducing toxin production. There are many difficulties at various levels in execution. Several in vivo studies show positive outcomes (Scarrott et al. 2015).

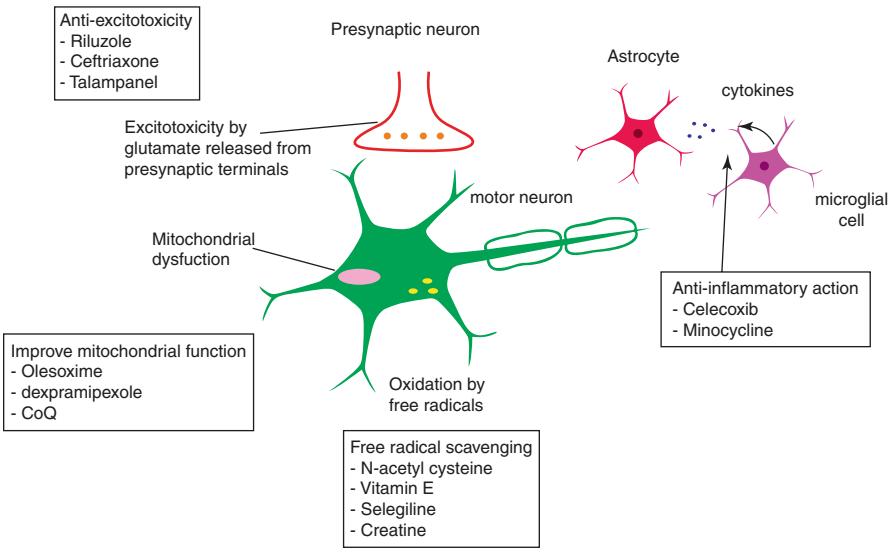

Fig. 2.4 Molecular pathways and candidate drugs in ALS

Table 2.9 Symptomatic therapy for ALS

Symptom	Therapy
Pain	NSAIDs, non-opioid analgesics, opioids, muscle relaxants, quinine sulphate, gabapentin, steroids, botulinum toxin and physical therapy (Chio et al. 2012)
Fatigue	Modafinil 100–300 mg daily (Rabkin et al. 2009)
Spasticity	Baclofen (both orally and intrathecally), tizanidine, benzodiazepines, botulinum toxin, dantrolene, and levetiracetam (Miller et al. 2009; Bedlack et al. 2009; Winterholler et al. 2002), hydrotherapy, cryotherapy, heat and ultrasound (Anderson et al. 2012)
Sialorrhoea	Anticholinergic medications, BOTOX in refractory cases
Sticky secretions	Increase fluids, propranolol 10 mg BID (Newall et al. 1996), anticholinergic drugs
Swallowing difficulties	Smaller bites, slowing down and avoiding talking, adding thickener to liquids, chin tuck or head turning to improve the ease and safety of a swallow, gastrostomy in cases of malnutrition/weight loss, long meal times, evidence for aspiration and dehydration (Miller et al. 2009; Czell et al. 2013)
Pseudobulbar affect	SSRIs, tricyclic antidepressants and SNRIs (Jackson and Rosenfeld 2006) in gradually increasing doses
Dependent oedema	Limb elevation, moving legs frequently, passive stretches, stockings, avoid diuretics (Borasio and Oliver 2000)
Urinary symptoms	Timed voidings; avoiding caffeine, alcohol and use of a urinal and condom catheter for men; oxybutynin 5 mg bid or tid; avoid anticholinergic medications
Constipation	Increased dietary fibre and water, fibre laxatives, stool softeners
Sleep disturbances	Therapy is cause based, bed adjustments, alternating pressure mattress, non-invasive ventilation, antidepressants (Miller et al. 2009)
Laryngospasm	Rapid change to the upright position, swallowing repetitively and breathing with slow exhalation through lips, benzodiazepines (Kuhnlein et al. 2008)

2.7.3 Symptomatic Therapy

This chronic debilitating disease has many symptoms which reduce the quality of life, and hence symptom management is a very important part of the therapy of ALS. These are listed in Table 2.9.

2.7.4 Exercises in ALS and Adaptive Equipment

Patients with ALS are recruited to the exercise program early in the course of the disease. The regimens are tailored to individual patient with the objectives of improving flexibility, increasing strength and providing aerobic benefits. A variety of adaptive equipment is available for improving the quality of daily life, for example, zipper pulls and Velcro fasteners, elastic shoelaces, strap fitted hair brush, long handled combs, page turning devices, large handled pens and hand splints (Paganoni et al. 2015).

2.7.5 Dealing with Patients and Families Having ALS

ALS is one of the most painful diagnoses for the clinician to make and for the family to accept. The initial diagnosis can have a very negative impact on the sufferers, and personally, we adopt a stepwise approach towards the disclosure. A second opinion may also be actively sought as the implications of the diagnosis are enormous. The disease progresses rapidly and new symptoms keep appearing. Families hence need multiple consultations which need to be organised. Often, the clinician himself finds himself at a dead end in trying to answer emerging questions and the tendency is to 'shut the door'. Herein is the need to appreciate that the families have no one else to go to, and it is important to continue the discussions and advice in the face of a seemingly hopeless situations.

2.7.6 Alternative Therapies and End of Life Issues

Patients with ALS often consider complementary and alternative therapies they read about on the Internet. Common types of alternative therapies considered for ALS include special diets, nutritional supplements, cannabis, acupuncture, chelation and energy healing. These need to be handled on individual basis depending upon the patient's belief in alternative systems and the perceived adverse effects. These can be variously tackled by offering autonomy to the patient, being supportive or as shared decisions (Bedlack et al. 2015).

It is being increasingly recognised that discussion of end of life issues with patients and families prepares them better for the eventuality. If the family can arrive at their preferred choice of actions, unnecessary interventions can be avoided. Discussion also helps them in facing the negative turns with less fear and apprehensions. Families vary remarkably in how they would like the situation tackled, which may be at time different from what the physician would think, and it is important to remember the patient autonomy. The aim should be to reduce suffering and maintain dignity. Caregiver stress needs full attention and at times pharmacological interventions (Connolly et al. 2015).

2.8 Prognosis

Factors associated with faster ALS progression are bulbar onset of symptoms, older age at symptom onset, shorter duration of symptoms and reduced forced vital capacity. On the other hand, patients who present with symptoms isolated to either end of motor neuron disease spectrum and regional ALS variants can have slower progression.

Genetic factors involved in prognosis are:

1. SOD1 Aso90Ala mutation: Good prognosis
2. SOD1 Ala4Val, C9orf72: Poor prognosis (Renton et al. 2014)

The mean survival ranges from 3 to 4 years, with survival after diagnosis being approximately 2 years. Longer survival (10 years) is seen in few of the patients, mostly in younger patients with relatively pure UMN involvement. Respiratory failure is the most common cause of death. Depressed consciousness due to hypercapnia occurs, and death itself is usually peaceful and occurs in sleep. Choking to death is unusual in ALS.

Key Points

When to suspect
- Pure motor
- Lower and upper motor neuron signs in the same segment (ALS)
- Widespread involvement
- Associated features like dementia, parkinsonism
- Only LMN involvement has wide differential diagnosis (Table 2.8)

How to investigate
- Electrophysiology showing three region involvement: Active and chronic de- and regeneration
- Exclusion of secondary causes (Table 2.6)

How to treat
- Supportive therapy
- Exercise program
- Riluzole
- Ventilator care
- End of life issues

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Hirayama Disease and Other Focal Amyotrophies

3

3.1 Hirayama Disease (HD)

3.1.1 Introduction

Focal forms of amyotrophies have been described. They include Hirayama disease (Hirayama 1991), crural amyotrophy (Gourie-Devi 2007) and brachial amyotrophic diplegia (Katz et al. 1999), and recently duropathies (Kumar 2012) have been characterized. These diseases affect only some of the anterior horn cells and may be progressive or self-limiting. The motor degeneration leads to disability and limitation of work. Hence recognising these forms is important. The recognition of their focal nature has a huge favourable impact on the prognosis. Out of these, Hirayama disease is seen frequently in Asia and is hence discussed first.

3.1.2 Epidemiology

Intriguingly, this disorder is known to predominantly affect young males belonging to Asian subcontinent with onset in teens or early 20s. It was first reported from Japan by Hirayama in 1959 (Hirayama et al. 1959). Later on, many cases were reported from Japan over next two decades. Similar cases of asymmetrical upper-limb amyotrophy were reported from India in 1980s and 1990s (Singh et al. 1980; Gourie-Devi et al. 1984; Virmani and Mohan 1985; Pradhan and Gupta 1997). Other Asian countries like Sri Lanka, Malaysia, Korea and Taiwan reported presence of this disorder. HD has been infrequently reported from Western countries like France, Germany, the United States, Italy, Poland and Switzerland; but it is known to be largely restricted to Asian subcontinent (Gourie-Devi 2007). It rarely affects females and only few case reports are available in literature (Hashimoto et al. 2012).

S.V. Khadilkar et al., *Neuromuscular Disorders*,
https://doi.org/10.1007/978-981-10-5361-0_3

In 1980, Singh et al. described 24 patients of juvenile non-progressive muscular atrophy and stressed on benign and self-limiting nature of the illness. Gourie-Devi et al. coined the term monomelic amyotrophy in 1984. She described that distal limb wasting was not only found in upper limbs but also 10 out of 23 patients had only lower limb involvement. Virmani and Mohan used the term "non-familial segmental spinal muscular atrophy in juvenile and young subjects". Pradhan and Gupta demonstrated similar clinical and radiological constellation of Hirayama disease and used the term juvenile asymmetrical segmental spinal muscular atrophy (JASSMA). Khadilkar et al. found that patients with upper-limb amyotrophy and dural changes on MRI had disproportionately longer necks as compared to controls. Thus, longer necks cause apparent shortening of dura and lead to tight dural canal during neck flexion.

3.1.3 Clinical Features

The classical description of Hirayama disease was first laid down by Hirayama in 1991 (Hirayama 1991). Selection criteria for the patients were as follows:

- Weakness and wasting predominantly in C7, C8 and T1 myotomes in one upper limb or asymmetrically in both upper limbs.
- Insidious onset in teens and early 20s.
- Initial fast progression followed by arrest of disease or relatively benign course.
- Irregular coarse tremors of affected hand(s).
- Mild transient worsening of symptoms on exposure to cold.
- Electromyographic evidence of chronic denervation in the clinically or subclinically affected muscles.
- Absence of objective sensory loss.

These features should strongly raise suspicion of Hirayama disease. This disease was described first only in males in teens or early 20s. Only few cases have been described in females. It is a largely a sporadic disease and only isolated familial occurrence has been reported in literature (Andreadou et al. 2009; Kajikawa et al. 2009; Pandey and Jain 2016). The onset of illness is insidious and progresses over a period of 1–3 years. Initial period of progression is followed by spontaneous arrest. However, it can progress up to a duration of 7 years but rate of progression is slower than the initial period of 3 years (Pradhan and Gupta 1997; Hirayama 2000). The cardinal symptoms of Hirayama disease are unilateral or asymmetric weakness and wasting of forearm and hands. Weakness and wasting predominantly occur in distribution of C7, C8 and T1 myotomes with sparing of muscles supplied by C5 and C6 roots. This results in "oblique amyotrophy", which occurs due to wasting of anterior and posterior compartments of forearm with sparing of brachioradialis (Hirayama and Tokumaru 2000) (Fig. 3.1). Another pattern of dissociated wasting is "reverse split hand" which has been recently described. In Hirayama disease, hypothenar muscles (abductor digiti minimi) are more affected than thenar (abductor pollicis longus)

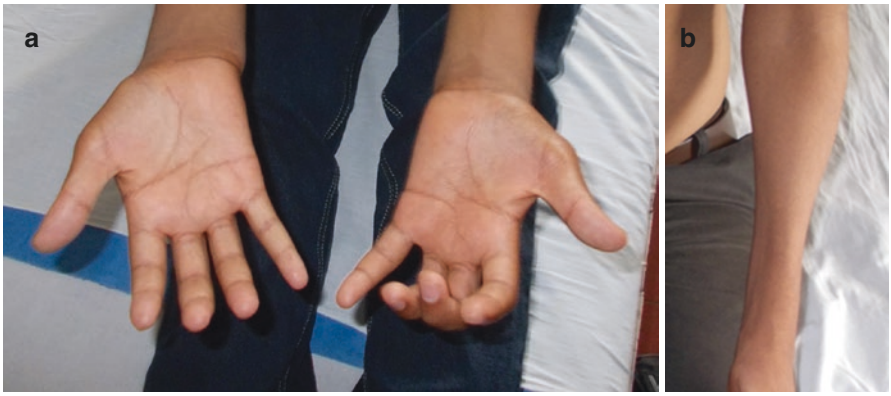

Fig. 3.1 (**a**) Atrophy of small muscles of hands and (**b**) oblique amyotrophy due to brachioradialis sparing in a patient with HD

muscles (Singh et al. 2016). In the authors' experience, some patients have finger extension weakness more than finger flexors and may actually present with "finger drop" in early stage of illness (Khadilkar et al. 2015). Although C7, C8 and T1 myotomes are predominantly affected, there have been case reports where C5 and C6 myotomes have been affected severely (Preethish-Kumar et al. 2016; Kim et al. 2016). Reports of scapular winging along with distal upper limbs are available (Holla et al. 2016). Rule of unilateral or asymmetrical involvement may not stand true in every case. In a case series of 106 patients, 10% were found to have bilateral symmetrical involvement. Hence, one should also consider Hirayama disease when there is bilateral symmetrical upper limb involvement and look for dural changes on flexion MRI (Pradhan 2009). Lower limb remains unaffected even till late stages of illness.

Other commonly occurring symptom is tremor of hands due to fasciculatory twitching of finger flexors and extensors (Hirayama 2000). A single case report has shown worsening of tremors immediately on lateral neck flexion but not on forward flexion. However, this phenomenon has not been widely studied (Koutsis et al. 2016). Most patients report aggravation of muscle weakness that worsens in cold environment. Patient may occasionally complain of sensory symptoms in hands and forearm but without any objective evidence of sensory loss. Deep tendon reflexes remain unaffected usually. In a case series of 73 patients, only 2 patients had knee jerk hyperreflexia but without any spasticity or extensor plantars (Wang et al. 2012). It is important to note that cranial nerves, neck muscles and sphincter functions remain unaffected.

3.1.4 Pathophysiology

Many theories have been postulated regarding pathogenesis of this unique anterior horn cell disorder. Despite postulations, exact cause of preponderance in young Asian males, self-limiting nature and restricted distribution to upper limbs of this

disorder remains unknown. Following factors are known to be associated or causally related to HD and are described below:

1. Anterior dural displacement causing dynamic compression of cord: In normal individuals, dura is strongly anchored posteriorly to subjacent lamina at foramen magnum, C2 and C3 at one end and coccyx at other end. Dura is attached loosely to the spine loosely in cervical region which creates a bit of dural slack. This slack helps dura to accommodate according to cervical spine curvature during neck flexion. In Hirayama disease, dural length is relatively shortened to vertebral column. This makes dura taut and creates a tight dural canal in flexion which no longer accommodates to curvature of spine during neck flexion (Iwasaki et al. 1987). Hence, there is anterior displacement of dura and enlargement of epidural space which causes dynamic compression of cervical spinal cord. These changes are quite significant and unique as MRI cervical spine in flexion in normal individuals does not show anterior displacement of dura. This dynamic compression along with dilated epidural venous plexus leads to microcirculatory changes in cord. As anterior horn cells are most susceptible to ischemia, it leads to slowly progressive degeneration of anterior horn cells. This is manifested by denervation in distribution of C7, C8 and T1 myotomes. One necropsy report shows shrinkage and necrosis of anterior horn cells of C5-T1, but particularly marked at C7 and C8 level (Hirayama et al. 1987; Pradhan and Gupta 1997; Hirayama 2000). As disease progresses, cord atrophy ensues. Thin cord is no longer compressed by anteriorly displaced dura which may explain its self-limiting nature. It is most popular theory as there is characteristic radiological demonstration of dural changes on neck flexion.
2. Disproportionate growth of cervical spine: Toma and Shiozawa postulated a novel mechanism. He postulated that disease is caused by disproportionate growth of spinal cord, dura and cervical roots. In normal individuals, cervical roots and their dural sheaths are slack. During neck flexion, the slackness of roots disappears and it prevents anterior displacement and compression of cord. In affected patients, due to imbalance between developments of spine, cord, roots and dura, the normal slackness of roots and its sleeves is lost. Hence, during neck flexion, cord along with dura is displaced and stretched anteriorly more towards affected side. This abnormal anterior displacement causes characteristic changes on MRI. This disorder occurs mainly in young males who are growing rapidly. Thus, he concluded that cause of this disorder depends on how the skeleton of the body grows during the adolescent period (Toma and Shiozawa 1995; Yada et al. 1984). In a recent study, it was observed that patients with upper-limb amyotrophy and characteristic dural changes had longer necks as compared to patients with upper-limb amyotrophy but without dural changes on flexion MRI. Thus, long neck appears to produce relative shortening of dura which creates tight dural canal in flexion. While this observation bears out Toma's theory of relative shortening of dura [due to longer cervical segment], it does not explain geographical distribution, male preponderance and spontaneous cessation of progression in Hirayama disease (Khadilkar et al. 2015).

3. Increased range of neck flexion: As mentioned earlier, forward displacement of dura during neck flexion is a key factor causing cord compression. Patients with Hirayama disease have increased flexed motion range of cervical spine as compared to controls which may contribute to pathophysiological changes. However, it was studied in 40 normal individuals which is too small a population to reach a conclusion (Xu et al. 2011).
4. Intrinsic anterior horn cell disease: In a case series of 40 patients with upper-limb amyotrophy, a proportion of patients (35%) did not show characteristic dural changes. Some patients had only snake-eye appearance. Hence, such patients with degeneration of anterior horn cells in cervical cord, but without dural shift, may point to existence of an intrinsic anterior horn cell disease (Khadilkar et al. 2015). Limited genetic studies are available which have documented absence of abnormalities in the SMN gene (Misra et al. 2005).
5. Toxin-induced amyotrophy: Toxins are known to be absorbed through skin and produce neurotoxicity. An observation is that this disease particularly affected young males who work with bare hands and are frequently involved in agricultural and industrial activities. It was hypothesized that some unknown toxin gets absorbed and produces amyotrophy. As amyotrophy ensues, patients become disabled to perform activities and thus disease remits by itself. This theory also explains geographical distribution as Asian population are more involved in agricultural and industrial activities with bare hands. However, it does not explain anterior dural displacement and asymmetry. However, no particular toxin is known to cause such an illness till date (Peiris et al. 1989).

3.1.5 Investigations

1. Plain X-ray cervical spine: Plain X-ray cervical spine in lateral position shows loss of normal lordotic curve in cervical region. In some cases, cervical kyphosis may be seen and it can further compromise cervical canal diameter. Range of cervical flexion motion (ROCFM) is increased in patients with HD as compared to unaffected controls. ROCFM is calculated as the angle between tangential lines drawn from posterior aspects of C2 and C7 vertebral body in flexion (Xu et al. 2011).
2. Electrophysiology: The most striking finding on electrophysiology is differential involvement of compound muscle action potential (CMAP) between ulnar-ADM and median-APB. In normal individuals, ulnar/median (U/M) CMAP ratio is 0.61–1.66. As ulnar mediated muscles are more severely affected than median innervated muscles in HD, U/M ratio is reduced. In a case series, U/M ratio is less than 0.6 in 74% while only 1 patient with ALS had lower ratios. This differential involvement can be helpful to distinguish between ALS and HD in early cases when UMN signs are not prominent. One may not be surprised to find mild ulnar conduction slowing across elbow (23%). Hence, severe reduction in ulnar-ADM amplitude should not be attributed to ulnar conduction slowing and unnecessary intervention can be avoided (Lyu et al. 2011). F-waves

remain normal in most patients except mild reduction in their frequency in minority of patients (Wang et al. 2012). In a recent study, neck flexion for 30 min has led to increase in number of repeater F-waves as compared to neutral position (Zheng et al. 2016). All SNAPs remain normal in all patients with HD. EMG helps to assess severity of denervation in clinically affected muscles and to detect the presence of denervation in apparently normal muscles on clinical examination. Ming-Feng Liao et al. documented changes of chronic denervation (high-amplitude, long-duration polyphasics) which were found most frequently in flexor carpi ulnaris, first dorsal interossei, abductor pollicis brevis and extensor digiti communis. Among proximal muscles, triceps is most commonly involved. Less frequently, deltoid and biceps can be involved. Changes of active denervation (fibrillation, fasciculations) are seen less frequently than chronic denervation in affected muscles. Other segments (bulbar, thoracic paraspinals and lumbosacral) do not show any abnormalities (Liao et al. 2016; Guo et al. 2012).

3. MRI cervical spine: The characteristic radiological changes are demonstrated on MRI cervical spine in neutral and flexion position. In neutral position, following changes can be seen (Fig. 3.2):
   (a) Loss of cervical lordosis and sometimes cervical kyphosis
   (b) Cord atrophy most prominent at C5–C6 level
   (c) Axial images show asymmetric flattening of cord
   (d) Hyperintense signal in anterior horn cell on axial T2 images (snake-eye appearance)

MRI cervical spine with neck flexion must be done to appreciate characteristic dural changes of Hirayama disease. Degree of neck flexion needed to demonstrate changes has been evaluated. Too little flexion may produce false-negative results while on the other hand full neck flexion may not be always possible, as standard MRI gantry allows limited space for forward movement of head on neck flexion. Hirayama et al. found 35 ° neck flexion to be optimal (Hou et al. 2012). Following changes found on flexion MRI are characteristic of Hirayama disease (Fig. 3.2):

- Anterior shifting of dura and prominent posterior epidural space.
- Anterior shifting of cord leads to compression of cord against vertebral body.
- Prominent epidural venous flow voids in posterior epidural space.
- Contrast administration shows enhancing crescentic mass in epidural space indicative of dilated venous plexus.

These changes are found in varying proportion in patients with Hirayama disease (Chen et al. 2004; Hassan et al. 2012). Some patients may demonstrate only dural changes without parenchymal changes. Few patients may have only snake-eye appearance without any dural shift. In a recent study, 65% of patients with upper-limb amyotrophy showed dural changes on MRI flexion. A subgroup exists which may not show typical dural changes. Such dural changes are diagnostic of Hirayama disease as they do not occur in any other disease or in normal individuals (Khadilkar et al. 2015).

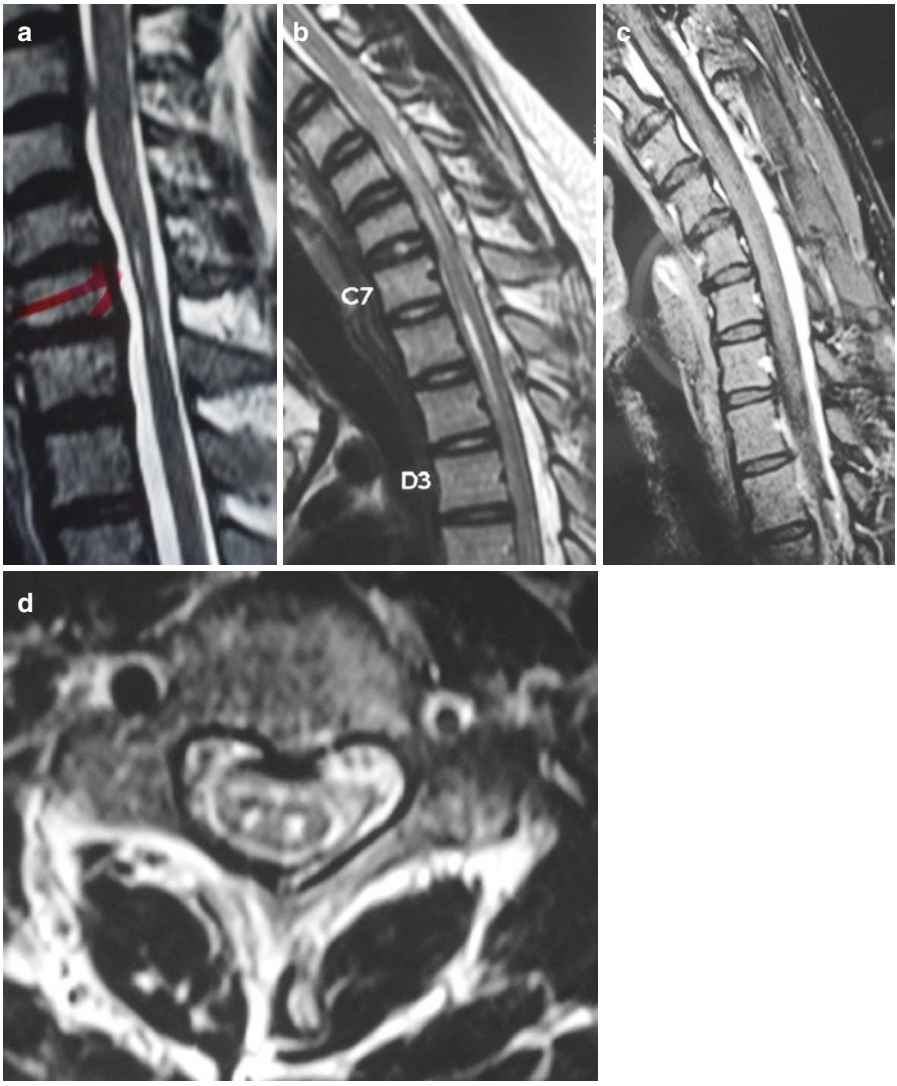

Fig. 3.2 (**a**) Cord atrophy at level of C5 and C6 and loss of cervical lordosis on neutral T2 sagittal images, (**b**) prominent epidural venous flow voids in posterior epidural space on T2 sagittal images, (**c**) contrast enhancement in posterior epidural space on post-contrast T1 fat sag images after 35° neck flexion and (**d**) axial T2 images showing asymmetric cord atrophy and hyperintense anterior horn cell signal (snake-eye appearance)

3.1.6 Differential Diagnosis

While considering diagnosis of Hirayama disease, one must also keep in mind that many diseases can present with weakness and wasting of upper limbs. Hence a systematic clinical and investigational approach is necessary when the clinician

Table 3.1 Differential diagnosis of HD with their key differentiating features

Diseases	Key differentiating features (apart from wasting and weakness)
Syringomyelia	Burning pain in back, suspended anaesthesia, dissociated sensory loss, painless wounds, bladder involvement and scoliosis
Leprosy	Painless ulcers, hypopigmented and hypoaesthetic patch and thickened nerves
High cervical cord compression	Deep tendon reflexes are often brisk in upper and lower limbs. Associated with posterior column dysfunction
Multifocal motor neuropathy with conduction block	Fifth-decade onset predominantly in males, progressive wrist drop, intrinsic muscle of hand weakness and presence of conduction block across affected segment
Neuralgic amyotrophy	Acute onset painful proximal > distal weakness followed by wasting
Kennedy's syndrome	Distal > proximal upper limb and lower limb involvement, tremors of hands, bulbar weakness and tongue fasciculations
Amyotrophic lateral sclerosis	In early cases, differential intrinsic hand muscle involvement. Thenar eminence and first dorsal interossei more affected than hypothenar eminence. Later into illness, tongue wasting, pyramidal signs particularly in affected segments, lower limb involvement and paraspinal fibrillations
Progressive muscular atrophy	Distal > proximal, asymmetric, lower limb > upper limb involvement with depressed reflexes
Distal spinal muscular atrophy	Predominantly symmetrical, distal > proximal, lower limb > upper limb weakness and wasting with preserved deep tendon reflexes
Focal myositis (cervicobrachial form)	Distal (finger extensors particularly) and proximal (trapezius and deltoid) weakness > wasting, no tremors. MRI muscle shows inflammatory changes in involved muscles
VLISFC (ventral longitudinal intraspinal fluid collection)	Previous history of flexion injury is often present. It presents as upper-limb amyotrophy without pyramidal signs. Associated feature is low-CSF-pressure headaches. MRI shows anterior epidural cyst

encounters upper-limb weakness and wasting. Confirmation of diagnosis of Hirayama disease helps not only in treatment but also in prognostication of illness. A number of conditions may mimic Hirayama disease as listed below in Table 3.1.

3.1.7 Management

As discussed above, dynamic compression of cervical cord with neck flexion and increased range of motion of cervical spine contribute to pathogenesis significantly. Hence, various methods have been tested to limit the flexion of cervical spine and thereby limit the progression of illness.

1. Cervical collar: Cervical collar was first used for therapy by Hirayama and Tokumaru in 1992 to limit the motion of cervical spine. In 2001, Tokumaru and Hirayama reported decline in mean duration of progression of illness from 3.2 ± 2.3 years in controls to 1.8 ± 1.2 years in Hirayama disease with the use of cervical collar. Hence, early intervention helps to minimize the functional disability of young patients (Tokumaru and Hirayama 2001; Cortese et al. 2015; Hassan et al. 2012). Pradhan and Gupta also found cervical collar to be useful during progressive stage of illness (Pradhan and Gupta 2001). While cervical

collar is an easy option, young patients find it socially disturbing and cumbersome to use it during routine activities. Also, cervical collar is a temporary method to limit neck flexion. In personal experience, early diagnosis and early measures to limit neck flexion, including collar, seem to have some impact on the evolution of this disease.

2. Surgical methods: In order to provide permanent solution, surgical intervention has been tried. Case reports of disease stabilisation with spinal fusion surgery (where vertebral bodies are fixed with plate and screws) are available but need to be interpreted with caution, as the natural history of HD is usually self-limiting (Paredes et al. 2014; Agundez et al. 2015). Another surgical approach is laminectomy plus duroplasty in which dura mater is tented with sutures posteriorly. This prevents forward shift of dura mater on flexion. This helps to preserve normal physiological motion in young patients with HD (Ito 2014). In advanced cases with severe atrophy, tendon transfer may help to significantly improve movements like gripping and pinching which can reduce disability in routine activities (Chiba et al. 2004). In personal experience, reverse curvature of the cervical spine is an important parameter in consideration of surgical candidates, as its presence changes the dynamics further.
3. Rehabilitation: Limb-strengthening exercises and splint support help to overcome disability in advanced stage of illness.

3.1.8 Prognosis

Hirayama disease is localised to upper limbs and progresses for a period of 3–4 years. Course is usually benign and lower limbs and bulbar muscles remain strong. If left untreated, it can lead to severe atrophy of hands. Hence, early detection and intervention are extremely helpful to limit the degree of disability.

3.2 Crural Amyotrophy (Wasted Leg Syndrome)

In this form of focal amyotrophy, there is wasting of unilateral lower-limb muscles. In 1980, Prabhakar et al. described 40 patients with wasted leg syndrome. In that series, most commonly affected were plantar flexors, dorsiflexors and quadriceps. Gourie-Devi described that similar to upper limbs, benign form of amyotrophy affects lower limb too. It affects young individuals, mostly between 15 and 25 years of age with male preponderance. In descending order of frequency, following muscles were affected: posterior compartment of leg (100%), anterior compartment of leg (81%), quadriceps (81%), peronei (45%), glutei (45%), adductors (37%) and hamstrings (36%). It has been noted that wasting is out of proportion to weakness in affected muscles. Patients usually note atrophy of lower limb due to pain while walking or is noted by others in 1/3rd of cases. Severe foot muscle involvement may cause foot drop. Intrinsic foot muscles usually remain unaffected. Electrophysiology shows neurogenic denervation in affected segments. Muscle biopsy shows neurogenic atrophy. MRI lumbosacral spine and cord do not show any changes. Course is usually benign and limited to involved limb. Prosthesis may be required to deal with

severe foot drop and quadriceps weakness (Prabhakar et al. 1981; Gourie-Devi 2007; Nalini et al. 2014).

3.3 Proximal Segmental Upper Limb Amyotrophy (Brachial Amyotrophic Diplegia)

As compared to Hirayama disease which affects distal (C7, C8 and T1) segments predominantly, brachial amyotrophic diplegia affects proximal (C5, C6) segments. The mean age of onset was 58 years in a case series of ten patients. Patients present with unilateral slowly progressive wasting and weakness of shoulder and arms. Over a period of time, it involves contralateral proximal segments and severe deficits leave behind bilateral flail arms (men in barrel). Deep tendon reflexes are usually hypoactive or normal. Distal upper limbs, bulbar, lower limb segments and pyramidal tracts remain normal till late into illness. Although it has a benign course, it leaves behind severe disability. EMG shows denervation in C5 and C6 myotomes. MRI may show features of anterior horn cell degeneration like cord atrophy and snake-eye appearance but dural changes on flexion are absent. While considering brachial amyotrophic diplegia, it is important to exclude diseases like ALS, HIV and MMN which can have serious therapeutic and prognostic implications. This is a form of segmental anterior horn cell degeneration but exact cause is not known (Katz et al. 1999; De Freitas and Nascimento 2000; Henning and Hewlett 2008; Van den Berg-Vos et al. 2003).

3.4 Case Study

Clinical details: A 40-year-old male presented with slowly progressive weakness and wasting of left upper limb over a period of 12-month duration. Weakness was more pronounced in proximal segments. Few months before presentation, he had noticed similar complaints in his right upper limb as well. There were no symptoms pertaining to lower limbs, cranial nerves, sphincters or sensory system. He did not have cold paresis, finger tremors, neck pain, radicular pain, fasciculations or headache. On examination, power in C5–C6 innervated muscles was MRC grade 3 while in C7, C8 and T1 innervated muscles was grade 4 on the left side. On the right side, power was grade 4 in C5 and C6 distribution. All tendon reflexes were normal. There was neither any sensory impairment nor long tract signs. Electrophysiology confirmed chronic severe denervation in C5 and C6 segments on left more than right side. There was mild-to-moderate chronic denervation in left C7, C8 and T1 myotomal distribution. SNAPs were normal.

Summary: This 40-year-old patient presented with slowly progressive, asymmetrical amyotrophy affecting left more than right, proximal more than distal segments without any sensory or pyramidal involvement. Should Hirayama disease be considered?

Discussion: Points in favour of HD are amyotrophy restricted to upper limbs in a male patient; but points away from the diagnosis are later age of onset and prominent proximal involvement.

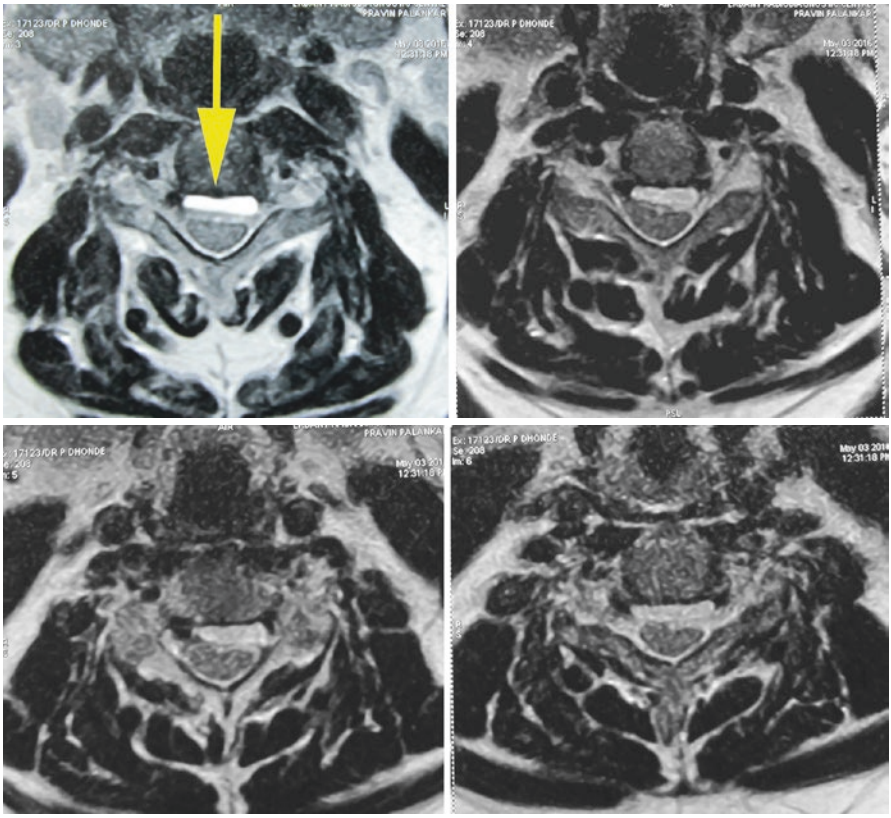

Fig. 3.3 Posterior displacement of cord due to CSF collection in anterior epidural space from C2 to upper dorsal level (*yellow arrow*) (courtesy: Dr. Pramod Dhonde, consultant neurologist, Nanded)

Other conditions which merit consideration are the following:

- Amyotrophic lateral sclerosis: Points in favour are upper limb amyotrophy in 40-year-old patient; points not in favour are absence of pyramidal signs and localised lower motor neurone signs in upper limbs. Full evolution may need 3–4-year follow-up.
- High cervical cord compression: Points not in favour are no sensory or pyramidal involvement.
- Segmental spinal muscular atrophy: Diagnosis of exclusion after ruling out other differentials.

MRI cervical spine was done with flexion and contrast. There was neither space-occupying lesion in neutral position nor any dural shift on flexion. However, there was posterior displacement of cord due to CSF collection in anterior epidural space from C2 to upper dorsal level (Fig. 3.3). These changes were consistent with newly described condition "ventral longitudinal intraspinal fluid collection (VLISFC)".

VLISFC: In 2008, Schmalbach et al. observed presence of ventrally placed epidural collection of CSF in patients with upper-limb amyotrophy (Schmalbach et al. 2008). Encysted fluid collection was believed to lead to chronic dynamic compression similar to Hirayama disease. Another proposed mechanism was that the posteriorly displaced cord leads to stretching of motor roots. The encysted fluid collection in ventral epidural space presumably occurs following a dural tear secondary to disc-osteophyte complex, spinal flexion injury or dural surgery in past. Upper-limb amyotrophy with or without brisk reflexes is the most common presentation of VLISFC (Deluca et al. 2011). Low-CSF-pressure headaches can occur due to intracranial hypotension secondary to dural tear. This condition has been reported in young as well as elderly males. Another associated condition is superficial siderosis secondary to microtrauma to the internal venous plexus in epidural space. Such patients can have associated symptoms of siderosis like ataxia and hearing loss (Kumar 2012). MRI of the cervical spine shows ventrally placed collection similar to CSF intensity in epidural space displacing the cord posteriorly. Radiological features of intracranial hypotension and superficial siderosis may be found depending on severity of illness (Foster et al. 2014; Kumar 2012). CT myelogram helps to determine the site of dural tear. These disorders have recently been clubbed together as "duropathies". It is important to recognise this group of conditions as repair of dural tear is known to lead to clinical stability and improvement (Kumar et al. 2012).

Key Points

Hirayama disease

When to suspect

- Young Asian male
- Distal asymmetrical upper limb weakness and wasting
- Sparing of brachioradialis, i.e. oblique amyotrophy
- Cold paresis

How to diagnose

- Flexion MRI of cervical spine with contrast showing dural changes
- Spinal cord atrophy
- Snake-eye signals

How to treat

- Cervical collar
- Surgery in selected patients

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Multifocal Motor Neuropathy

4

4.1 Introduction

MMN is immune-mediated demyelinating neuropathy affecting motor fibres. It was described by Parry and colleagues on a set of patients with pure motor neuropathies, cramps, fasciculations and preserved reflexes. They pointed out that the presence of multifocal conduction blocks in these patients distinguished it from motor neuron disease (Parry and Clarke 1988). Around the same time, reports of its association with anti-GM1 serum antibodies became available, and treatability was demonstrated (Pestronk et al. 1988). However, neither the presence of conduction block nor anti-GM1 antibodies is necessary to diagnose MMN (Pakiam and Parry 1998).

4.2 Epidemiology

The estimated prevalence of MMN is 0.6–2 per 100,000 populations (Nowacek and Teener 2012).

4.3 Clinical Features

Most cases present in the fifth decade, but the age of symptom onset ranges from childhood to the eighth decade of life. Male to female ratio is approximately 3:1. Patients present with chronic asymmetric distal limb weakness, atrophy and fasciculations affecting the distal arm more frequently than the leg, usually in the distribution of individual nerves with limited or no sensory symptoms (Nowacek and Teener 2012). Most patients present with insidious intrinsic hand weakness, wrist drop or foot drop which progresses over the course of several years to involve other limbs. Rarely, it starts acutely or affects cranial-innervated muscles (Galassi

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et al. 2012; Galassi and Girolami 2012). Lack of atrophy in weak muscles should heighten the suspicion of MMN. Deep tendon reflexes may be diminished but are often normal in unaffected nerves and occasionally can be brisk. Clonus, spasticity and extensor plantar responses are not observed. Cold paresis has been infrequently reported. This is rather unexpected because demyelination, a feature of MMN, generally improves symptomatically in cold. It was hypothesised that cold paresis in MMN does not reflect demyelination only but may indicate the existence of inflammatory nerve lesions resulting in permanently depolarised axons that are barely able to conduct at normal temperatures but fail at lower temperatures (Straver et al. 2011).

More recently, sensory loss of a variable degree has been described in patients with otherwise typical MMN. Five of 11 cases fulfilling AANEM diagnostic criteria MMN at the onset of disease developed sensory loss associated with electrophysiological sensory abnormalities while being treated with IVIg. The mean time to appearance of objective sensory signs was 7.2 years, being preceded by intermittent paraesthesias in the same nerve territories as the motor involvement in 3/5 cases. Anti-GM1 IgM antibodies were positive in four patients. Though these five cases overlap with MADSAM, they were closer to MMN on clinical and therapeutic grounds. Therefore, the Joint Task Force of the European Federation of Neurological Societies/Peripheral Nerve Society 2010 revised guideline on MMN requires that there would not be any objective sensory abnormality except for minor vibration sense abnormalities in the lower limbs but allows for sensory signs and symptoms that may develop over the course of MMN. Type 1 diabetes, Hashimoto's thyroid disease and celiac disease are known to be significantly more prevalent in family members of patients of MMN than controls (Cats et al. 2012). MMN is described in patients receiving anti-tumour necrosis factor (TNF), monoclonal antibody and infliximab, which is a commonly prescribed medicine for ulcerative colitis, Crohn's disease and rheumatological conditions (Rowan et al. 2015).

4.4 Pathophysiology

Sensory nerve biopsies from patients with MMN are usually unrevealing, and biopsies are not done routinely in the evaluation of MMN (Bouche et al. 1995; Corse et al. 1996). While one study has shown evidence for demyelination without inflammatory cell infiltrates at the site of motor conduction block (Kaji et al. 1993), another pathological study of seven patients demonstrated multifocal axonal degeneration without any overt signs of demyelination (Taylor et al. 2004). These findings suggest that an antibody-mediated attack directed against components of axolemma at nodes of Ranvier could cause transient conduction block that is rapidly reversible with IVIg and axonal degeneration and regeneration.

4.5 Investigations

4.5.1 CSF Study

The CSF protein level in most cases of MMN is normal, and a significantly elevated CSF protein level should suggest an alternate diagnosis.

4.5.2 Electrophysiology

Although motor conduction block (CB) has been considered the electrophysiologic hallmark of MMN, some otherwise typical MMN cases have no detectable CB. This may be due to proximal location of the conduction block making it difficult to confirm electrophysiologically or to the activity dependence of these blocks (Fig. 4.1). Conduction block is not essential to the diagnosis of MMN if other features of demyelination like prolonged distal latencies, temporal dispersion, slow conduction velocity and delayed or absent F waves on motor NCS are detected (Katz et al. 1997). The AANEM consensus criteria for definite or probable MMN include patients without objective sensory loss and with normal sensory nerve conduction velocity across the same segments with demonstrated motor conduction block and normal sensory nerve conduction studies on all tested nerves, with a minimum of three nerves tested.

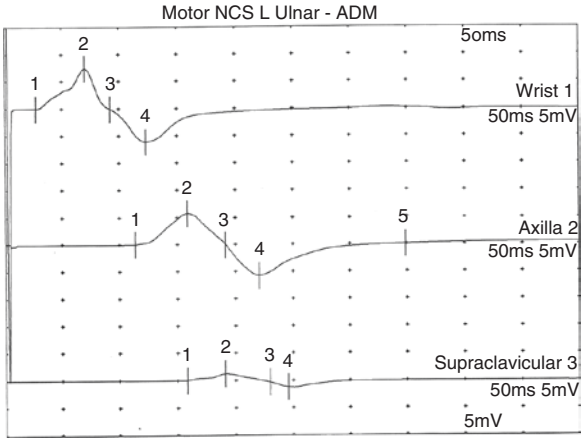

Fig. 4.1 Motor conduction of the *left ulnar nerve* showing a conduction block on stimulating in the supraclavicular region. Note the drop in the area by 80% with no increase in the duration. Ulnar SNAP was normal, and wrist stimulation recorded potentials from the elbow and Erb's point, implying normal sensory function (Courtesy: Dr. Khushnuma Mansukhani, Bombay Hospital, Mumbai)

4.5.3 Imaging

Peripheral nerve imaging is a potentially powerful technique to distinguish MMN from ALS. T2-weighted MRI scans are known to show increased signal intensity associated with a diffuse nerve swelling of affected nerves (Van den Berg-Vos et al. 2000). High-resolution ultrasound scan cross-ional area values of the median nerve in the forearm and the ulnar nerve distal to the sulcus have been shown to be significantly enlarged in patients with MMN as compared to ALS (Jongbloed et al. 2016).

4.5.4 Antibodies

Anti-GM1 IgM antibodies are positive in almost half of the patients. Pestronk and colleagues recently identified serum IgM binding, using covalent antigen linkage to ELISA plates, to a disulphated heparin disaccharide (NS6S) in 43% of 75 motor neuropathy cases with mostly distal predominant asymmetric arm weakness and objective sensory loss of the distal legs in 28 cases. The value of NS6S IgM antibody in clinical practice is yet to be determined.

4.6 Differential Diagnosis

Patients with MMN may develop secondary axon loss with resultant denervation atrophy leading to a misdiagnosis of amyotrophic lateral sclerosis (ALS). However, weakness in the latter is in a myotomal pattern, whereas in MMN, it follows a peripheral nerve distribution. Axonal form of MMN has only axonal features on electrodiagnostic studies but responds to IVIg (Fisher et al. 2004).

4.7 Management

Response to treatment is no different between patients with or without conduction block (Azulay et al. 1999; Ellis et al. 1999). While corticosteroids and PE may improve rare MMN patients, most MMN cases have deteriorated with these treatments (Carpo et al. 1998; Donaghy et al. 1994). Most MMN patients respond to IVIg with improvement typically beginning within several days and lasting several weeks to months. Most responders show improvement after the first treatment and will have a long-term response to IVIg. However, over time, axon loss and disability may accrue (Taylor et al. 2000). Though there is no data from prospective randomised controlled trials, there are several reports of benefit from rituximab, a monoclonal anti-CD20 antibody. Stieglbauer K et al. reported quantitative strength improvements by 13–22% in the rituximab group at 1 and 2 years and remained essentially unchanged in the control subjects.

This was associated with 45% reduction in anti-GM1 antibody titres at 2 years. However, most patients with initial benefit developed recurrent weakness at 3–9 months after treatment and received a second set of treatment and then one infusion every 10 weeks to maintain benefit (Stieglbauer et al. 2009). Intravenous cyclophosphamide is effective in over 70% of MMN cases. In patients with significant deficits who are unresponsive to IVIg or rituximab, monthly pulses of intravenous cyclophosphamide 0.5–1.0 mg/m^2 with or without PE for 6 months can be given. The role of subcutaneous IVIg (SCIg) in MMN is uncertain. A large prospective randomised controlled trial of SCIg in MMN has yet to be done.

According to Cochrane review in 2015, mycophenolate mofetil did not produce significant benefit in terms of reducing the need for IVIg or improving muscle strength in MMN. Trials of other immunosuppressants need to be undertaken (Umapathi et al. 2015).

4.8 Prognosis

The IVIg response declines over a period of time, between 3 and 7 years into the therapy. While IVIg often has a significant benefit initially, the response declines over time. Nonresponders have longer disease duration before the first treatment. Independent determinants of worse weakness and disability were axon loss and longer disease duration without IVIg. Early IVIg treatment may postpone axonal degeneration and permanent deficits (Cats et al. 2010).

4.9 Case Study

Clinical details: A 44-year-old lady typist presented with the complaints of gradually progressive difficulty in extending the right index finger, of 8–10-month duration. It progressed over the next 4 months to involve the other fingers of the right hand. She also noticed wasting of thenar aspect of the right hand and difficulty in performing fine motor activities and gripping with the right hand. The patient did not have history of weakness in the left upper limb or lower limbs. There was no history of pain, sensory symptoms, fasciculations or difficulty in speaking and swallowing. On examination, she had finger drop of the right index, middle and ring finger due to finger extensor weakness (Fig. 4.2). There was no wrist drop and wrist extensors were normal. Small muscles of the right hand were weak. Deep tendon reflexes of both upper limbs were absent, and lower limb reflexes were elicited on reinforcement. Sensory examination was entirely normal.

Summary: A 44-year-old lady having gradually progressive right-sided finger drop with depressed tendon reflexes without any pain, sensory loss, fasciculations or cranial nerve involvement.

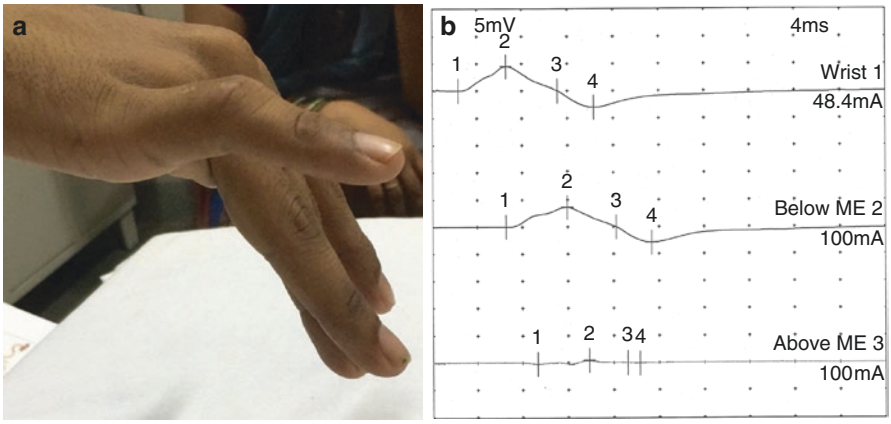

Fig. 4.2 (**a**) Finger drop and (**b**) electrophysiology showing conduction block across ulnar nerve

Discussion: 'Finger drop' has limited differential diagnosis such as atypical variants of demyelinating neuropathies, focal forms of inflammatory myopathies and posterior interosseous neuropathy, and rarely patients having facioscapulohumeral dystrophy and slow-channel myasthenia can exhibit finger drop.

Investigations revealed normal creatine kinase levels and thyroid profile. Electrophysiology showed normal sensory nerve conduction studies. Motor nerve conduction studies showed partial conduction blocks along right median and ulnar nerves from stimulation at Erb's point with prolonged F waves (Fig. 4.2). There were no changes of demyelination along the forearm and wrist in affected nerves; hence, brachial plexus or proximal segments of nerves were unlikely to be involved. Sensory conduction parameters were entirely normal. MRI neurography was done to evaluate proximal nerves or plexus lesion, which showed thickening of the brachial plexus, reminiscent of CIDP. Despite anti-GM1 antibody being absent, possibility of MMN was considered as there was multifocal affection of motor nerves which complete the sparing of the sensory segments. Patient responded well to initial IVIg administration and is presently on maintenance doses.

Key Points

When to suspect

- Pure motor distal involvement often in the upper limb
- Gradual progression
- Adulthood presentation

How to diagnose

- Motor conduction blocks
- Other features of demyelination
- Normalcy of sensory segment
- Anti-GM1 antibodies
- MR neurography showing swelling of affected nerves

How to treat

- IVIg
- Other immunosuppressants like cyclophosphamide and rituximab

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Acute Motor Axonal Neuropathy

5

5.1 Introduction

The first cases of axonal GBS were reported by Feasby and colleagues (Feasby et al. 1986). In 1990, Yuki and colleagues reported on two Japanese patients who presented with acute pure motor axonal polyneuropathy and raised concentrations of IgG antibodies against GM1 after an episode of *C. jejuni* enteritis. They suggested that there was an association between these features (Yuki et al. 1990). In a later study in northern China to investigate a summer epidemic of an acute paralytic disorder amongst children in rural areas, 36 patients having acute pure motor polyneuropathy showed electrophysiological evidence of axonal degeneration and raised concentrations of protein in CSF (McKhann et al. 1991). The researchers initially described this disorder of the distal motor nerve terminal or anterior horn cells as the Chinese paralytic syndrome, which was distinct from GBS. Another axonal subtype of GBS is acute motor and sensory axonal neuropathy (AMSAN), in which neurophysiological and pathological findings indicate axonal degeneration of motor and sensory nerves (Griffin et al. 1996).

5.2 Epidemiology

The frequency of AMAN in the whole GBS population varies substantially between countries: it is rare in many European and in North American countries but particularly prevalent in East Asia and Central and South America. Worldwide, a substantial proportion of patients with GBS have AMAN. In an Indian study of 51 patients, application of the criteria of Ho and colleagues showed 44 (86%) cases with the AIDP pattern and four (8%) with the electrodiagnosis of AMAN (Ho et al. 1995; Kalita et al. 2008). Infection with *C. jejuni* is the most frequent antecedent in patients with AMAN, and, therefore, the prevalence might differ between countries according to the predominance of *C. jejuni* infection.

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5.3 Clinical Features

Compared to AIDP, patients having AMAN progress more rapidly and reach peak of weakness earlier, cranial nerve involvement is less frequent and neuropathy tends to be pure motor. Sensory examination is normal, although up to 10% of patients report positive sensory symptoms, such as pins and needles in the distal limbs. Tendon reflexes are preserved, and patients might develop hyperreflexia at the peak of illness or during the early recovery phase. Around 10% of patients have normal or exaggerated tendon reflexes throughout the entire disease course, and in about 5% tendon reflexes are preserved at initial examination but become diminished at the peak of the disease (Yuki et al. 2012). Autonomic dysfunction, such as hypertension, prominent fluctuation of blood pressure or heart rate and hyperhidrosis, is not seen or, if present, is mild (Asahina et al. 2002).

5.4 Pathophysiology

Four criteria must be satisfied to conclude that an autoimmune disease is triggered by molecular mimicry (Ang et al. 2004):

- Establishment of an epidemiological association between the infectious agent and immune-mediated disease
- Identification of T cells or antibodies directed against the patient's target antigens
- Identification of microbial mimicry of the target antigen
- Reproduction of the disease in an animal model

AMAN subsequent to *C. jejuni* enteritis fulfils all four criteria (Yuki et al. 2001). The pathology in AMSAN is consistent with an antibody-mediated pathogenesis in the dorsal and ventral roots (Griffin et al. 1996). Sodium channel dysfunction has been postulated as the ionic mechanism of conduction blockade or slowing in AMAN (Kuwabara et al. 2002; Kuwabara et al. 2003).

5.5 Investigations

5.5.1 Electrophysiology

Consistent with the clinical manifestation of pure motor polyneuropathy, sensory nerve conduction studies show values in the normal range and low distal compound muscle action potentials with preserved sensory nerve action potentials in the same nerve segments. These characteristics are strongly suggestive of AMAN. When the electrodiagnostic criteria for chronic inflammatory demyelinating polyneuropathy were first introduced, the cut-off values for acute demyelination differed notably from those for chronic demyelination (report of a joint task force of the European

Federation of Neurological Societies and the Peripheral Nerve Society – first revision 2010). Generally, less strict cut-off values are used for AIDP. Because AMAN was originally thought to be simple axonal degeneration, the cut-off values for AIDP were reasonable at that time. Later studies showed, however, that the additional features of AMAN indicate microstructural changes at the nodes and paranodes of motor axolemma (Susuki et al. 2007), which could account for the rapidly reversible nerve conduction abnormalities in patients with AMAN, but the cut-off values in the conventional criteria do not seem to reliably differentiate the two subtypes. The electrodiagnostic criteria, therefore, need to be reconsidered (Uncini et al. 2010; Uncini and Kuwabara 2012).

Although the immunopathogenesis and pathophysiology of AMAN have been established, several issues are still controversial. First, the electrodiagnostic criteria were proposed on the assumption of simple axonal degeneration in AMAN, and, therefore, they do not seem to distinguish between AIDP and AMAN with certainty. Sequential electrodiagnostic studies would provide new insights into the pathophysiology and electrodiagnosis of GBS (Uncini and Kuwabara 2012). Other unresolved issues include the identification of underlying mechanisms for motor-selective involvement.

5.5.2 Antibodies

AMAN and AMSAN share a common immunological profile and pathology, and, therefore, AMSAN is deemed to be a severe form of axonal GBS (Uncini and Yuki 2009). Patients with AMSAN have antibodies against GM1, GM1b and GD1a following infection with *C. jejuni* (Yuki et al. 1999).

5.6 Differential Diagnosis

For differential diagnosis of AMAN, please refer to chapter on GBS.

5.7 Management

For general management, please refer to chapter on GBS. Two preliminary reports have suggested that for patients with AMAN, immunoglobulin therapy is better than plasma exchange (Kuwabara et al. 2001; Hughes et al. 2012), although this finding was not confirmed in a subsequent study (Hadden et al. 2001).

5.8 Prognosis

Two patterns of recovery are seen: some recover within days, whereas others have slow and poor recovery. The rapid recovery is caused by resolution of conduction block, and the poor recovery is associated with extensive axonal degeneration at the

nerve roots (Kuwabara et al. 1998). In the experience of authors, the severity of the weakness at nadir seems to be one of the important prognostic factors, those having more than MRC grade 3 power fare better. The clinical course of AMSAN is generally more severe than that of AMAN, with slower recovery and a poorer prognosis.

Key Points

When to suspect

- Acute, rapidly evolving, pure motor neuropathy.
- Reflexes may be retained or brisk.

How to investigate

- Electrophysiology: reduced CMAPs, normal SNAPs and maintained nerve conduction velocities
- Antibodies: GM1

How to treat

- IVIg or PE
- Supportive care
- Rehabilitation

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Facioscapulohumeral Dystrophy

6

6.1 Introduction

Facioscapulohumeral dystrophy (FSHD) is characterised by progressive muscle weakness and wasting exhibiting a clinical pattern evident from early stages of the disease. It affects facial, periscapular and humeral muscles early in the disease course, a constellation which is not commonly seen in other myopathies (Tawil 2006). The progression can be marked by periods of rapid deterioration followed by stabilisation (Stübgen and Stipp 2010). FSHD is inherited as autosomal dominant disease; however, up to 30% cases are sporadic, arising from de novo mutations (Tawil et al. 2015).

6.2 Epidemiology

Two French physicians – Landouzy and Dejerine – initially described a family with progressive wasting disorder, probably giving the early description of FSHD (Landouzy and Dejerine 1885). The prevalence of FSHD is 1 in 20,000 individuals worldwide (Padberg 2004).FSHD is the third most common form of muscular dystrophy. It accounts of 2–3% cases of muscular dystrophy in India (Khadilkar 2008). The median age of onset of FSHD is around 17 years, but with a wide range varying at the most extreme from infancy to the seventh decade (Tawil et al. 2015). A significant variability in clinical expression is present, even amongst affected members of the same family.

6.3 Clinical Features

There are three characteristics of the distribution of muscle weakness in FSHD (Table 6.1):

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Table 6.1 Clinical features of FSHD

Site of involvement	Clinical features	
Facial involvement	As many as two thirds of patients are unaware of facial involvement (Walton and Nattrass 1954). The most evidently affected muscles are orbicularis oculi and orbicularis oris Difficulty closing the eyes – sleeping with eyes open leads to dryness, uncomfortable feeling and gritty eyes in the mornings Slight staring appearance without proptosis in awake state Difficulty to whistle, suck or blow balloons. Most patients never realise the link between these mild inconveniences and later development of shoulder weakness. Asymmetric facial involvement is common and most evident on smiling	Facial wasting Unlined face Mild stare Sometimes facial weakness is very asymmetrical and appears unilateral, but careful examination reveals subtle weakness on the other side too
Upper limb	Difficulty in abducting arms with resultant difficulty in keeping objects on to high shelves, difficulty in combing hair and easy fatigue The main muscles involved are the latissimus dorsi, serratus anterior, pectoralis, rhomboids, trapezius, supraspinatus, infraspinatus and deltoid Asymmetric winging of scapula The shoulders tend to slope forward with straight clavicles and pectoral muscle atrophy. The characteristic pattern causes chicken wing scapulae for which at times medical attention is sought	Winging of scapulae Usually seen at rest and exaggerates on arm manoeuvres; scapulae ride and can be seen anteriorly Popeye sign – wasting of arm muscles with sparing of forearm muscles Poly-hill sign: 1. Upward projection of superior angle of scapula tenting the wasted trapezius 2. Prominent laterally projected acromioclavicular joint 3. Prominent inferolateral part of deltoid muscles 4. Prominent muscles of extensor compartment of forearm (Pradhan 2002)
Lower limb involvement	Typical affection of peroneal compartment presenting as asymmetric foot drop	FSHD involves peroneal compartment before the pelvic girdle, but vice versa is known (Lemmers et al. 2014; Upadhyaya and Cooper 2004)
Abdominal muscles	Protuberance of the abdomen and exaggerated lumbar lordosis	Lower abdominal muscles are selectively involved, resulting in Beevor's sign (upward displacement of the umbilicus upon flexion of the neck in a supine position)

Table 6.2 Extramuscular involvement in FSHD

Systemic involvement	Salient features
Respiratory system	Respiratory difficulty can occur in severe cases because of skeletal abnormalities (scoliosis, hyperlordosis). There is no difficulty with swallowing or difficulty to expectorate Assessment of pulmonary function can be difficult because of the great difficulty forming a decent seal around most devices measuring airflow. In infantile FSHD, presumed primary diaphragmatic or intercostal muscle involvement can cause respiratory failure (Nakagawa et al. 1996)
Hearing	Hearing impairment in FSHD was first described by Small in 1968. It can be profound and in some families could be the presenting feature of FSHD (Taylor et al. 1982) Significant hearing loss is a feature of early onset and sporadic cases of FSHD; it is seen consistently in adult-onset FSHD (Upadhyaya and Cooper 2004)
Vision	Coats' disease (retinal vasculopathy) Retinal vasculopathy: failure of vascularisation of the peripheral retina, telangiectatic blood vessels and microaneurysms can be demonstrated by fluorescein angiography in 40–60% of affected individuals (Padberg et al. 1995). Patients with large deletions should be screened with indirect ophthalmoscopy Retinal vascular tortuosity may represent a milder manifestation of Coats' disease
Cardiac	Symptomatic cardiac disease is rare in FSHD. Minor rhythm abnormalities are known, but their clinical significance is yet undetermined (Tawil et al. 2015)
Pain	Pain occurs in up to 79% of patients with FSHD. The most common sites of pain are, in descending order, the lower back, legs, shoulders and neck. About 10.8% of patients had clinically significant pain (Tawil et al. 2015)

- Early involvement of the face
- Involvement of upper girdle before the lower girdle
- Striking asymmetry of muscle involvement

Apart from muscle weakness, other neurological and systemic features are known to occur in patients with FSHD (Table 6.2).

6.4 Pathophysiology

The gene for FSHD has been mapped to 4q35 locus which contains several KpnI repeats. Despite having distinct genotypes, FSHD1 and FSHD2 have an identical molecular basis that results from the aberrant expression of the DUX4 gene in skeletal muscle (Table 6.3). Inappropriate expression of DUX4 and its transcriptional targets in skeletal muscle can result in apoptosis, impaired muscle regeneration and induction of an immune response.

Table 6.3 Genetics of FSHD

	Gene	Test method	Mutations	Frequency
FSHD1	D4Z4	Targeted mutation analysis	Deletion of critical number of D4Z4 repeats	95%
		Haplotype analysis	Analysis to confirm that the D4Z4 contraction mutation occurred on a permissive haplotype	
FSHD2	D4Z4	Methylation analysis	D4Z4 hypomethylation (<25% methylation)	<5%
	SMCHD1	Sequence analysis	*SMCHD1* sequence variants	<5%

Lemmers et al. (2014)

Table 6.4 Investigations in FSHD

Tests	Significance
Serum creatine kinase (CK)	Normal to mildly elevated. Usually does not exceed three to five times the upper limit of the normal range. Serum concentration of CK over 1500 IU/L suggests an alternate diagnosis (Lemmers et al. 2014)
EMG	Mild myopathic potentials
Muscle biopsy	Nonspecific chronic myopathic changes. Mononuclear inflammatory reaction is present in up to 40% of individuals. Rarely, the inflammatory reaction is intense enough to suggest an inflammatory myopathy Some biopsies show angulated fibres. Nowadays, muscle biopsy is required only in those individuals in whom FSHD is suspected but not confirmed by molecular genetic testing (Lemmers et al. 2014)
Molecular genetic testing	Derepression and dysregulation of *DUX4* (within the macrosatellite repeat D4Z4) FSHD1: contraction of the D4Z4 repeats FSHD2: mutations in *SMCHD1* (Lemmers et al. 2014)

6.5 Investigations

The following investigations are helpful to confirm the diagnosis of FSHD and rule out its close differentials (Table 6.4).

Molecular diagnosis is done by southern blotting with probe p13E11 followed by double digestion of genomic DNA by EcoRI and BlnI restriction enzymes. EcoRI fragment size varies between 50 and 500 kb in normal individuals and is less than 35 kb in FSHD patients due to decreased KpnI repeats (Upadhyaya et al. 1997).

6.6 Differential Diagnosis

The clinical phenotype of FSHD is characteristic, and the differential diagnosis is limited to only a few other myopathies (Table 6.5).

Table 6.5 Differential diagnosis of FSHD

Differential diagnosis	Key distinguishing features
Myofibrillar myopathy (previously called desmin-storage myopathy): can simulate FSHD as it results in slowly progressive proximal + distal muscle weakness, autosomal dominant inheritance	Distal muscles more affected than proximal Also affects heart (cardiomyopathy) causing conduction defects, congestive heart failure Weakness starts distally and then progresses proximally Muscle biopsy helps to differentiate it from FSHD
Inclusion body myositis: slow progressive proximal weakness and atrophy and causes foot drop due to peroneal weakness. Asymmetry	Onset is usually after 50 years of age Males are more commonly affected than females Weakness of finger flexors and quadriceps is characteristic
GNE myopathy: progressive wasting and weakness of peroneal compartment	Begins in late teens or early adulthood Presents with distal weakness in lower limbs (foot drop) Occasional patient can have prominent upper girdle weakness as well
Mitochondrial myopathies: familial progressive muscle weakness	Multisystem involvement: short stature, visual diminution due to optic atrophy and pigmentary retinopathy rather than Coats' disease, external ocular muscle involvement
Polymyositis: progressive proximal muscle weakness Advanced cases can present with food drop	Inflammatory disease: associated with pain Response to steroids Begins in proximal muscles of lower limbs–hip extensors Can affect bulbar muscles
Scapuloperoneal muscular dystrophy: slowly progressive proximal + distal muscle weakness, autosomal dominant inheritance	MYH-7 related, rare disorder Molecular genetic testing allows definitive diagnosis and differentiation from FSHD
Calpainopathy: gradually progressive weakness of shoulder and pelvic girdle with ankle dorsiflexor more weaker than plantarflexors	No facial weakness Symmetric proximal >distal weakness It has three forms: 1. Pelvifemoral variety: most frequent phenotype, weakness first starts in pelvic girdle and then involves shoulder girdle 2. Scapulohumeral variety 3. Asymptomatic hyperCKaemia

6.7 Management

The goal of therapy in FSHD is to improve muscle strength or function or both.

6.7.1 Physiotherapy

Aerobic exercise in FSHD appears to be safe and potentially beneficial, as has been shown in many other muscle diseases. It improves muscle mass and strength (Tawil et al. 2015).

6.7.2 Surgery

Scapular fixation helps in significant improvement in shoulder range of motion. Fixation is generally considered after the skeletal growth is completed. Haemothorax or pneumothorax, pain, infection, nonunion and reduced lung capacity are rare issues with this surgery (Tawil et al. 2015).

6.7.3 Pharmacotherapy

Albuterol, corticosteroid and diltiazem have been tried but not found to be effective in increasing muscle strength or stopping the progression of disease (Tawil et al. 2015). In personal experience, corticosteroids seem to help a proportion of patients who enter a phase of rapid deterioration with further elevation of serum CK levels. Oral prednisolone in the doses of 0.5 mg per kg or thereabouts can be initiated and used over ensuing few weeks, depending upon the progress.

6.7.4 Management of Pain

Pain compounding muscle weakness can have a significant impact on QOL. Nonsteroidal anti-inflammatory agents have been used for acute pain and antidepressants or antiepileptics for chronic musculoskeletal pain (Tawil et al. 2015).

6.8 Prognosis

Disease progression is generally slow, with affected individuals often experiencing long periods of static weakness interspersed by sudden and painful periods of muscular deterioration. Females are usually less symptomatic than males and older patients are usually more severely affected. The size of the disease-associated 4q35-D4Z4 repeat array also influences disease severity, with smaller number of repeats (1–3 units) often associated with more severe affection (Tawil et al. 1996). Early age at onset is associated with early loss of ambulation. Almost 15–20% of FSHD patients become wheelchair bound with advancing disease and muscle weakness by 50 years of age; others remain fairly asymptomatic (Padberg 1982). Despite the morbidity associated with this disorder, there is surprisingly little evidence for reduced life span.

6.9 Case Study

Clinical details: A 29-year-old male, born of nonconsanguineous marriage, presented with asymmetrical proximal upper limb weakness of 10 years duration. Initially, he noticed weakness of left arm, and 2 years later, right upper limb became weak. Since 6 years, he has developed weakness of both lower limbs. Due to proximal weakness, he had difficulty in getting up from sitting position. He used to trip

and fall frequently while walking, suggesting distal foot weakness. For all the 10 years, he had noticed inability to close eyes well and was aware of his inability to blow a whistle. There was no history of sensory complaints nor any bowel and bladder involvement, and no other family member was suffering from similar symptoms. On examination, patient had following signs

- Bifacial, neck, trapezius, scapular and asymmetrical (left > right) arm weakness (Fig. 6.1a, b)
- Scapular winging (Fig. 6.1b)
- Selective wasting and sparing of particular group of muscles, i.e. 'poly-hill sign' and 'Popeye arm appearance' (Fig. 6.1b, c)
- Prominent anterior axillary fold suggestive of weakness of pectoral group of muscles (Fig. 6.1c)
- Beevor's sign and exaggerated lumbar lordosis suggestive of weakness of trunk muscles (Fig. 6.1d, e)

Summary: A 29-year-old patient presented with asymmetrical proximal upper limb > > lower limb (proximal + distal) weakness and wasting with scapular winging, prominent bifacial and neck weakness.

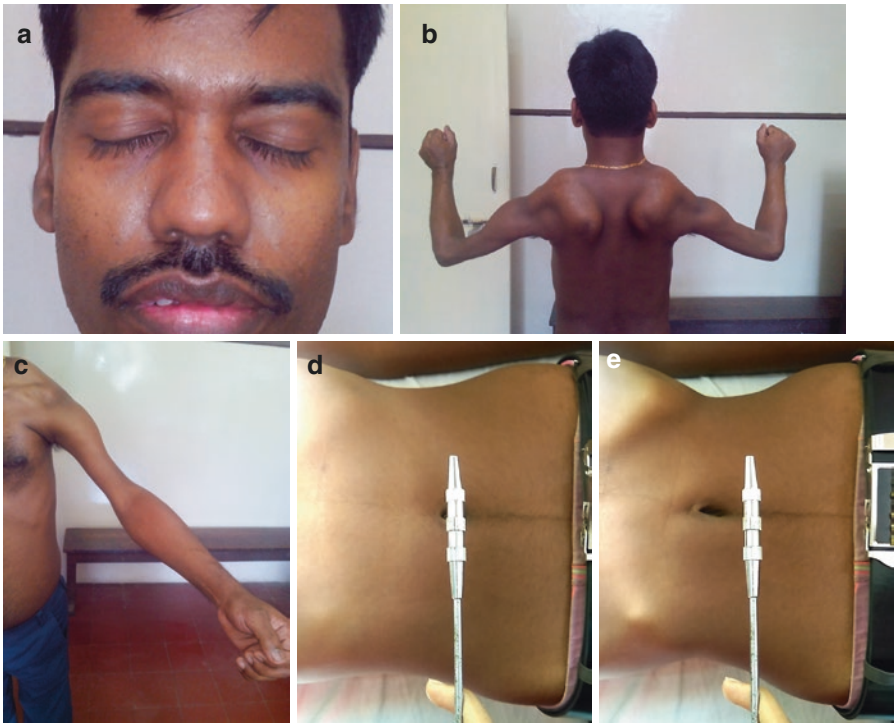

Fig. 6.1 Clinical signs in FSHD (**a**) bifacial weakness, (**b**) scapular winging, riding and poly-hill sign, (**c**) Popeye sign, (**d**, **e**) Beevor's sign

Table 6.6 Patterns of weakness in different muscle diseases

Muscle diseases with asymmetrical onset	Muscle diseases with prominent and early facial weakness	Muscle diseases with proximal upper limb and distal lower limb weakness	Muscle diseases with prominent scapular winging
FSHD Anoctaminopathy	FSHD Myotonic dystrophy	FSHD Scapuloperoneal syndrome EDMD	FSHD Calpainopathy Dystrophinopathy Sarcoglycanopathy

Discussion: Due to striking asymmetry and prominent proximal upper limb and distal lower limb weakness and wasting, anterior horn cell disorders would come to mind, in addition to FSHD. The pattern of weakness, wasting, scapular winging and presence of bifacial weakness favours FSHD. Muscle diseases usually present as symmetrical, proximal lower limb more than upper limb weakness with mild involvement of distal limb, neck and facial muscles. However, few muscle diseases deviate from such typical presentation (Table 6.6).

Investigations revealed CK value of 1700 and myopathic potentials on NEE. Based on clinical phenotype, possibility of FSHD was very likely. Genetic test for confirmation of diagnosis was not available locally. Although genetic tests are required for confirmation of muscular dystrophies, certain phenotypes are very specific to particular muscular dystrophies, e.g. FSHD and myotonic dystrophies.

Key Points

When to suspect

- Autosomal dominant transmission.
- Chronic progressive facial weakness.
- Scapular winging and riding.
- Popeye sign.
- Poly-hill sign.
- Beevor's sign.
- Asymmetry is very common unlike most myopathies.

How to diagnose

- Elevation of CK.
- Biopsy may show inflammatory cells.
- Genetic studies (Table 6.3).

How to treat

- Physical therapy
- Albuterol, corticosteroids, diltiazem
- Scapular fixation

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Progressive Muscular Atrophy

7

7.1 Introduction

Progressive muscular atrophy (PMA) is a sporadic, lower motor neuron (LMN) disorder due to degeneration of anterior horn cells and brainstem nuclei. It is an uncommon form of motor neuron disease. PMA is differentiated from amyotrophic lateral sclerosis (ALS) by absence of upper motor neuron (UMN) involvement in former. PMA retains its separate identity, but may have links to ALS, as a proportion of patients with initial diagnosis of PMA progress to ALS. Subclinical UMN dysfunction in PMA has been found pathologically, electrophysiologically and radiologically in a proportion of patients (Liewluck and Saperstein 2015). Hence, it is still unclear whether PMA is a unique variant of motor neuron disease (MND) or belongs to ALS spectrum (Kim et al. 2009). A number of diseases can present with pure lower motor neuron involvement and mimic PMA but are treatable. Hence, establishing diagnosis of PMA can have diagnostic and therapeutic implications (Sanderson et al. 2015).

7.2 Epidemiology

The term 'progressive muscular atrophy' was first used by Aran and Duchenne in a patient with presumed myopathy, but was proven to be of neurogenic origin on autopsy, by Cruveilhier. Charcot commented upon the fact that PMA had only LMN involvement, while ALS had both UMN and LMN involvement. From that time, PMA became a distinct clinical entity. Due to its rarity, sizable collections of PMA patients are very few. The largest study (Kim et al. 2009) deals with various aspects of PMA and documents that PMA accounts for a small proportion (2.5–11%) of all MNDs. PMA is far more common in men than women (3:1–7.5:1). Mean age of onset is from 63.4 ± 11.7 years. Majority of the literature on PMA is from Western world, and its incidence is 0.02 per 100,000 (Liewluck and Saperstein 2015). Published data from India on PMA is very scarce.

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7.3 Clinical Features

Patients usually present with slowly progressive LMN features such as flaccid limb weakness, atrophy, fasciculations and depressed reflexes (Statland et al. 2015). PMA is asymmetrical and distal in onset, beginning either in upper or the lower limb. Rare case reports of axial onset have been reported (de Carvalho et al. 2007). Symmetrical proximal limb weakness resembling myopathic pattern can occur in up to 20% of cases (Kim et al. 2009). Unlike ALS, bulbar muscles are spared at onset (Van den Berg-Vos et al. 2009). However, later in course of illness, they can get affected in up to 40% of patients. UMN signs are absent at the onset. But in a case series of 962 patients, Kim et al. observed that 22% of patients developed UMN signs by 61 months of observation. These patients perhaps represent LMN onset of ALS. In patients who develop UMN signs, the requirement for non-invasive respiratory support is more likely than patients who exhibit only LMN features (Kim et al. 2009). Unlike spinal muscular atrophy (SMA), PMA has older age of onset, sporadic occurrence and asymmetrical distal onset (Rowland 2010). Cognitive functions are spared in PMA (Wicks et al. 2006). In a prospective study, mean survival duration was 56 months which is somewhat longer than ALS. The 3-year and 5-year survival rate is 67–73.3% and 40.7–45%, respectively (Visser et al. 2007; Kim et al. 2009). PMA is a clinical diagnosis, and no biochemical tests help in its confirmation. Diagnosis requires clinical and electrophysiological features of LMN dysfunction in two or more different myotomal distributions (bulbar, cervical, thoracic and lumbosacral), evidence of disease progression over time and the exclusion of other LMN syndromes (Liewluck and Saperstein 2015).

7.4 Pathophysiology

PMA is caused by degeneration of lower motor neuron in spinal cord and brainstem nuclei. Post-mortem studies have identified inclusion bodies in anterior horn cells similar to ALS. Most common protein found in inclusion bodies is 43 kDa transactive responsive sequences DNA-binding protein (TDP-43) (Geser et al. 2011). In a proportion of patients, FUS-positive inclusions were found. Despite absence of UMN signs on clinical examination, post-mortem studies have shown degeneration of corticospinal tracts in 50–85% of patients (Liewluck and Saperstein 2015; Tsuchiya et al. 1999). Hence, pathological findings in PMA were similar to that found in ALS. A number of genetic mutations are associated with anterior horn cell degeneration, e.g. SOD1, SMN1 and C9orF72 (Cervenakova et al. 2000). However, majority of these genetic abnormalities are absent in PMA. At present, exact pathogenesis of PMA is not clearly known (Liewluck and Saperstein 2015).

7.5 Investigations

There are no specific investigations to confirm diagnosis of PMA. It is not surprising to find mild elevations in CK, and CK levels up to 735 have been described in a case series (Van den Berg-Vos et al. 2009). Electrophysiology helps to

confirm active and chronic denervation in affected as well as apparently normal segments and rule out focal demyelinating lesions in a given setting. Nerve conduction studies show normal sensory conductions and low to normal compound motor amplitude potentials (CMAP) (Sorenson 2012). In one study, it was found that differential involvement of intrinsic muscles of hands can help to differentiate amongst various anterior horn cell disorders. Abductor digiti minimi CMAPs were severely involved in PMA and spared as compared to abductor pollicis brevis in ALS (Kim et al. 2015). Needle electrode examination shows signs of active denervation in form of fibrillations, fasciculations and unstable MUPs in bulbar, cervical, thoracic paraspinals and lumbosacral segments in varying proportions (Sorenson 2012; Visser et al. 2008). Diffusion tensor imaging shows reduced fractional anisotropy along corticospinal tracts, and transcranial magnetic stimulation elicits prolonged central motor conduction time in patients with PMA suggesting subclinical UMN involvement (Van der Graaff et al. 2011; Kim et al. 2009).

7.6 Differential Diagnosis

PMA is a diagnosis of exclusion. Some immune neuropathies, e.g. multifocal motor neuropathy (MMN), and paraneoplastic neuropathies can result in pure LMN-type weakness and are treatable. Amongst degenerative ones, spinal muscular atrophies, bulbospinal atrophy and Hirayama disease form close differential diagnoses of PMA. Besides these two large groups, rarely, amyotrophy can be a dominating feature in conditions like Tay–Sachs disease, porphyria and anti-Ma2 syndrome. In such rare instances, additional clinical signs can help (e.g. cerebellar signs for Tay–Sachs disease, abdominal pain for porphyria, features of encephalitis for anti-Ma2 syndrome) (Albertyn et al. 2014; Waragai et al. 2006; Deik and Saunders-Pullman 2014).

7.7 Management

Currently, there is no specific treatment for PMA. No treatment trials for PMA are available, but experts suggest that it should be treated on same lines as ALS.

7.8 Prognosis

Amongst various anterior horn cell diseases, PMA follows ALS in terms of accumulating disabilities. Several factors have been shown to be associated with shorter survival, including axial onset, involvement of more segmental regions, ALSFRS-R at diagnosis less than 38, baseline forced vital capacity (FVC) less than 80% of the predicted value and a sharp decline in FVC within the first 6 months. Patients with PMA who have weakness restricted to distal or proximal muscles for at least 4 years typically have a more favourable prognosis.

Key Points

When to suspect

- Chronic progressive, pure motor, lower motor neuron disease
- Weakness, fasciculations, atrophy and areflexia
- Normal sensations
- Absence of upper motor neuron signs (note overlap with ALS)

How to investigate

- Electrophysiology: chronic and active de- and reinnervation
- Diagnosis of exclusion (Table 7.1)

How to treat

- Supportive and rehabilitative therapy

Table 7.1 Differential diagnosis of PMA with their key differentiating features

Disease	Key differentiating features
Spinal muscular atrophy	Younger age of onset, autosomal recessive inheritance, proximal, symmetrical LMN involvement. Unlike PMA, genetic testing is diagnostic in form of SMN 1 gene deletion
Multifocal motor neuropathy	Fifth decade onset predominantly in males, progressive wrist drop, intrinsic muscle of hands weakness and presence of conduction block across affected segment. Unlike PMA< biochemical tests can help in diagnosis, e.g. raised CSF protein and anti-GM1 antibodies
X-linked spinobulbar muscular atrophy	Bulbar onset, perioral fasciculation, features of androgen resistance like gynaecomastia, associated sensory neuropathy, tremors and prolonged 10-year survival rates. CK levels are elevated. Elevated CAG trinucleotide repeats are diagnostic
Distal myopathies	Lower limb predominant, differential weakness, slowly progressive. No bulbar, respiratory weakness and poses no imminent risk of death
Hirayama disease	It is important to differentiate from upper limb onset PMA in early stages. Male predominant, teens to early twenties onset, slowly progressive, self-limiting illness restricted to upper limbs amongst Asians. MRI shows characteristic dural changes
Distal SMA	Early onset, predominantly symmetrical distal > proximal, lower limb > upper limb weakness and wasting with preserved deep tendon reflexes
Amyotrophic lateral sclerosis	Lesser male preponderance than in PMA. It can have bulbar involvement at onset and prominent UMN signs and have rapid progression. Mean survival is less than 3 years as compared to 5 years in PMA. Electrophysiology shows higher ADM/APB CMAP ratio than PMA
Plexopathies	See Chaps. 31 and 32

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Post-polio Syndrome

8

8.1 Introduction

Acute paralytic poliomyelitis has a monophasic course which leaves behind residual neurological deficits. However, a proportion of survivors develop new-onset, progressive symptoms in affected as well as apparently unaffected limbs. These symptoms occur many years after the initial illness. Early observations on this delayed deterioration can be found in literature as early as 1875 [Charcot]; however, the condition got established in 1980s as 'post-polio syndrome (PPS)'. Today, poliomyelitis might be on verge of eradication, but old polio survivors continue to be at risk of PPS. It is important to recognise this condition as it can cause severe neurological deficits and mimic other conditions.

8.2 Epidemiology

Poliomyelitis had assumed epidemic proportions in the nineteenth century. With effective vaccination, there was dramatic drop in new cases in mid-twentieth century. As long-term data on polio survivors was studied, it was realised that some of them had delayed deterioration. In 1980s and 1990s, 'post-polio syndrome (PPS)' was accepted as a new medical condition (Trojan and Cashman 2005; Bridgens et al. 2010; Baj et al. 2015). It is expected that there are 15–20 million survivors of polio worldwide (Wilson 2005). India has been recently declared polio-free, but it is expected to house close to 8 million cases of PPS (Bhandari 2014). Polio survivors have been reported from every country, and they continue to face risk of developing PPS. Prevalence of PPS widely ranges from 20 to 75% amongst polio survivors worldwide. It is important to highlight that PPS can occur in survivors of paralytic as well as non-paralytic polio illness (post-polio fact sheet 2012; Nee et al. 1995). Few predictive/risk factors for development of PPS have been identified. These include a greater severity of acute paralytic poliomyelitis, older age at onset,

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muscle and joint pains in the acute event, residual impairment after recovery from poliomyelitis, older age, female gender, longer interval since the acute illness and increased physical activity (Trojan and Cashman 2005).

8.3 Clinical Features

The interval between acute poliomyelitis and PPS can range from 8 to 71 years with a mean duration of 36 years. This long duration represents period of recovery and stabilisation before the compensatory changes eventually burn out. In various observational studies, female sex is found to be more associated with risk of PPS. Common symptoms are pain, fatigue and weakness. Fatigue is the most common and disabling symptom. Fatigue is felt as a sense of exhaustion and decreased exercise tolerance, and it worsens as day progresses. A proportion of patients experience mental fatigue in form of decreased concentration, increased daytime naps and increased rest periods (Trojan et al. 2009; Berlly et al. 1991; Viana et al. 2013). PPS is gradually progressive but subacute onset and stepwise progression has been noted. Weakness usually occurs in limbs affected at the time of acute poliomyelitis, but clinically unaffected muscles during that time can also get affected. This suggests subclinical motor neuron loss at the time of acute poliomyelitis. Both muscle and joint pains contribute to disability. Muscle pain is felt as aching sensation, soreness, burning and cramps. Multiple joint pains can occur due to bursitis, osteoarthritis or tendonitis. Other associated symptoms are muscle atrophy, cold intolerance, change in sleeping pattern, bulbar weakness and respiratory distress. Such neurological features cause severe impairment of mobilisation and day-to-day activities (Bertolasi et al. 2012; Trojan and Cashman 2005).

March of Dimes (2001) provided diagnostic criteria for the post-polio syndrome which are widely employed. These criteria rely on establishing an acute poliomyelitis event, a prolonged period of partial or complete recovery and maintenance of good functionality (usually over 15 years) followed by progressive muscle weakness in areas which were originally affected. Allowance has been made for new symptoms and signs as well. While using these criteria, it is extremely important to exclude all other possible causes, neurological, medical or orthopaedic in nature.

8.4 Pathophysiology

It is noteworthy that new neurological deficits occur many years after stabilisation of acute illness. Various hypotheses have been postulated, but the exact cause of PPS is still unknown. Some possible mechanisms are mentioned below.

- Distal degeneration model: It is by far the most accepted mechanism. After acute poliomyelitis, there is compensatory sprouting of terminal axons and reinnervation of denervated muscle fibres. These enlarged motor units continue to undergo remodelling to reinnervate muscle fibres over a period of few years. At last, a time comes when this balance is lost and enlarged motor units start degenerating. This probably explains long interval before development of PPS. However, involvement of clinically unaffected muscles still remains to be well explained.
- Autoimmunity and cofactors: Level of immune complexes, various antibody levels and cellular activity remain normal in PPS. At present, there is no evidence of immune mechanisms operating in the development of PPS.
- Reactivation of persistent poliovirus infection: In a proportion of PPS patients, poliovirus genomes and poliovirus-specific oligoclonal IgM bands have been found in CSF. This may point towards persistent poliovirus infection. Family members of patients with PPS do not exhibit such markers indicating that PPS patients may be noninfectious. It is still not clear how persistent viral infection leads to a progressive disorder (Dalakas 1995; Emeryk et al. 1990).

8.5 Investigations

PPS is often a clinical diagnosis. Investigations seldom help to confirm it but are needed to assess severity of motor loss and exclude its differentials. Electrophysiology helps to confirm lower motor neuron involvement in form of normal SNAPs, reduced CMAPs and chronic denervation on EMG. It also helps to exclude other causes. It can also detect unrelated disorders like entrapment neuropathies and radiculopathies that can cause additional neurological deficits. Motor unit number estimation (MUNE) gives detailed estimation of output of single motor unit as CMAP may remain normal despite ongoing axon loss (Farbu et al. 2006). Investigational studies have shown presence of IgM antibodies in CSF, but its significance in establishing diagnosis is not fully known (Dalakas 1995). Other investigations to rule out its differentials are discussed below.

8.6 Differential Diagnosis

A number of conditions cause isolated peripheral motor dysfunction due to motor neuron or peripheral nerve disorders. They may have associated pain and fatigue. Some mimics are treatable and some are partially modifiable. Hence it is important to develop a systematic clinical and investigational approach towards patients presenting with pain, fatigue and weakness (Sanderson et al. 2015) (Table 8.1).

Table 8.1 Differential diagnosis of PPS with their key distinguishing features

Disease	Key differentiating features
Polymyalgia rheumatic (PMR)	Pain, morning stiffness for more than 45 min in proximal joints but sparing distal joints and elevated ESR. Pain in PPS becomes worse with activity and as day progresses and can affect distal joint too. PMR do not develop weakness or atrophy. Steroid is treatment of choice
Fibromyalgia	Pain and tenderness in 11/18 points with fatigue. Generalised involvement, no weakness/atrophy favours fibromyalgia. Coexistence of both diseases is known (Trojan and Cashman 1995). SNRIs help to relieve symptoms
Radiculopathy/plexopathy	Acute-onset sensorimotor deficit in a well-defined segment. Electrophysiology and radiology confirm radicular or plexus involvement
Focal amyotrophy like Hirayama disease	Male predominant, painless slowly progressive, self-limiting illness restricted to upper limbs. MRI shows characteristic dural changes
Amyotrophic lateral sclerosis	Amyotrophy and muscle cramps involving bulbar, cervical, thoracic paraspinals and lumbosacral segments with pyramidal signs
Cramp fasciculation syndrome	Muscle cramps, fasciculations, myokymia but no weakness or atrophy. Benign course and improves with carbamazepine
Multifocal motor neuropathy	Fifth decade onset predominantly in males, painless progressive wrist drop, intrinsic muscle of hands weakness and presence of conduction block across affected segment

8.7 Management

No specific therapeutic interventions are currently available to tackle the disability of the survivors, and hence we need to rely on rehabilitative and supportive symptomatic measures.

8.7.1 Rehabilitation

It is important to formulate exercise programs for patients with PPS as submaximal exercise results in functional improvement, while intensive training may be harmful. The following exercise programs have been found to be effective. Submaximal aerobic exercises cause reduction in maximum heart rate and increased endurance by 28%. Submaximal fractionated isometric and isokinetic programs have been found to be beneficial than intensive training schedules in increasing muscle strengths (Agre et al. 1996). Muscle strengthening programs results in gain in muscle strength. Aquatic training in warm climate is one of the treatments of choice for PPS as it helps in improving

strengths as well as improving pain (Willen and Scherman 2002). It is important to appreciate that fatigue can worsen with continuous muscle activity. Use of orthosis helps to prevent contractures, improves mobility and decreases fatigue (Tiffreau et al. 2010). Attempts at preventing excessive weight gain are useful, as weight gain is considered to have detrimental effects in patients suffering from PPS (Farbu et al. 2006).

8.7.2 Pharmacological Measures

Many medications such as pyridostigmine, prednisolone, amantadine and modafinil have been tried but found to be ineffective. Trials of IVIG show that it might be helpful in reducing pain but has no impact on overall outcome. It has been observed that a subgroup of patients with age less than 65 years, lower limb weakness and severe pain are more likely to experience reduction in pain after IVIg therapy (Ostlund et al. 2012). Like IVIg, lamotrigine also reduces pain and fatigue in some patients. At present, no medication is available that can alter the course of illness (Koopman et al. 2015). Fatigue is most disabling symptom, but therapy is seldom helpful (Aguila-Maturana and Alegre-De Miquel 2010).

8.8 Prognosis

PPS is a slowly progressive disorder. It is rarely fatal, but its course is dangerous in patients with respiratory and bulbar involvement. Most patients report progressive deterioration in strength. Physical training often helps to improve strength and endurance, but its effects are not long-lasting. As mentioned above, some medications help in reducing pain to some extent. Fatigue remains the most resistant symptom (Trojan and Cashman 2005).

Key Points

When to suspect

- Polio in childhood
- Quiescent period of many years
- Increasing lower motor neuron dysfunction

How to investigate

- Electrophysiology showing chronic denervation with new activity
- Exclusion of other causes (Table 8.1)

How to treat

- Rehabilitation

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Part II

Symmetric Proximal Weakness

Duchenne and Becker Muscular Dystrophies

9

9.1 Introduction

DMD is the most frequent and best studied early-onset muscular dystrophy. It was described as pseudohypertrophic muscular dystrophy by Gaetano Conte (1836) and Meryon (1851). It was named after Duchenne who discussed and wrote about it in 1868.

9.2 Epidemiology

DMD begins in early childhood and runs a relatively rapid, progressive course. The incidence is about 1 in 3500 live male births. Being an X-linked recessive trait, it is seen almost exclusively in males, but manifesting females have been documented. When female patients manifest the disease, they may have only one X chromosome, as occurs in the Turner syndrome (XO), and that chromosome carries the Duchenne gene, or the Lyon principle may be operative, i.e. there is inactivation of the unaffected paternal X chromosome allowing expression of the mutated Duchenne protein from the maternal chromosome in large proportion of embryonic cells. Autosomal translocation of material from X chromosome is another mechanism. In India, more than one affected child in a family is not uncommon due to cultural and social issues (Khadilkar 2008).

S.V. Khadilkar et al., *Neuromuscular Disorders*,
https://doi.org/10.1007/978-981-10-5361-0_9

9.3 Clinical Features

9.3.1 DMD (Table 9.1)

Clinical manifestations of DMD with respect to time span have been mentioned in Table 9.1.

9.3.2 Becker Muscular Dystrophy (BMD)

BMD is less severe clinical presentation of dystrophinopathy. The onset is much later, mean age 12 years (range 5–45 years). Patients usually walk well into adult life. The weakness follows the pattern of DMD, and cardiac involvement is less frequent.

9.3.3 Examination of the Mothers of Affected Boys

Majority are asymptomatic. However, a minority of carriers have clinically evident muscle weakness, the manifesting carriers. Some carriers experience muscle pains or cramps without weakness. Cardiac involvement is usually subclinical, but an occasional carrier may have severe cardiac failure. It is believed that carriers do not have reduced life expectancy.

Table 9.1 Clinical manifestations in time spans

Years of age	Clinical features
Birth–2 years	Usually asymptomatic, sometimes delayed motor milestones
2–5 years	Recurrent fall, never good at running, toe walk, Gower's manoeuver (Fig. 9.1a, b, c, d, e), waddle due to weakness of the gluteus medius, calf hypertrophy, valley sign (Pradhan 2002): simultaneous hypertrophy of deltoid superolaterally, infraspinatus inferomedially and wasting of posterior axillary fold (Fig. 9.2a) Occasionally present with language or global developmental delay or asymptomatic hyperCKaemia
6–7 years	Paraspinal muscles weaken (lordosis visceroptosis). Waddle more obvious. At this stage, the quadriceps is often weakened, leading to episodes of knee buckling and falls
9–12 years	More difficult to stand, taken to the wheel chair (Jones et al. 2003), multiple contractures (achilles tendon, iliotibial band, knee and hip areas), kyphoscoliosis, respiratory dysfunction. Deep tendon reflexes are depressed in weak muscles, and ankle reflex continues to be elicited till very late in the disease
Cardiac muscles	Dilated cardiomyopathy, cardiac conduction defects (less common) (Perloff 1984)
Respiratory muscles	Restrictive lung disease, vital capacity begins to diminish around 10 years of age, reducing at the rate of 10%/year, obstructive sleep apnoea, sleep disturbances (Suresh et al. 2005)
Intelligence	Average tends to be lower, lower values of the verbal IQ, attention-deficit disorders (Leibowitz and Dubowitz 1981)

Fig. 9.1 Gower's sign: patient rising from ground (**a, b, c, d, e**)

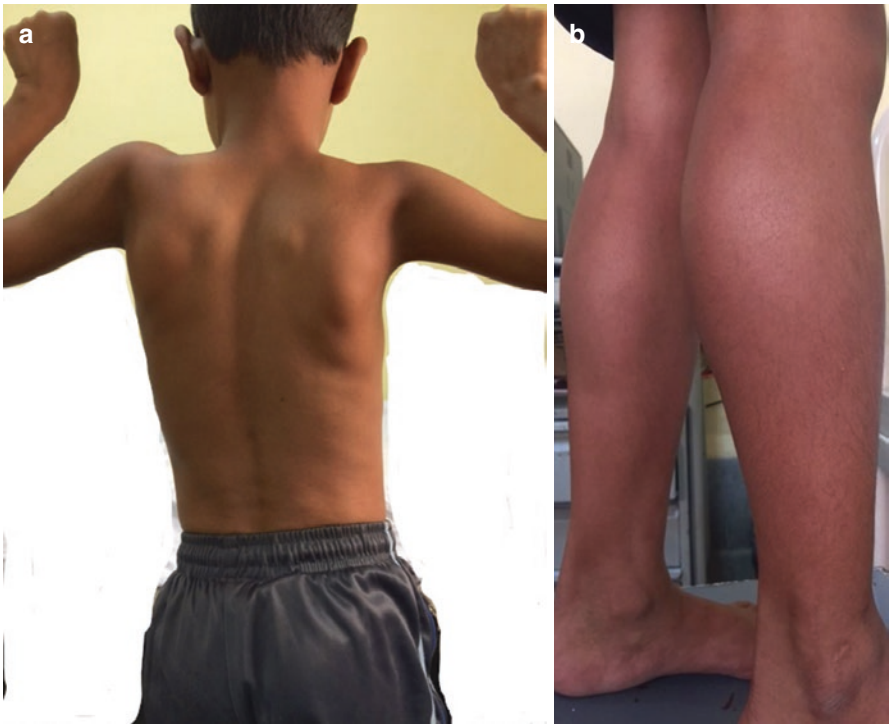

Fig. 9.2 (**a**) Valley sign and (**b**) calf hypertrophy in a patient with DMD

9.3.4 Other Phenotypes Associated with Dystrophinopathies

There are exercise intolerance, myalgia, exertional myoglobinuria, isolated cardiomyopathy and asymptomatic hyperCKaemia. Comparable clinical progression is seen in familial cases with few exceptional cases showing phenotypic variability with same in-frame mutation.

9.4 Pathophysiology

Mutation on short arm of X chromosome at Xp21 produces non-functional dystrophin leads to DMD. It is one of the largest genes, spanning 2.5 MB (0.1% of total genome) with high spontaneous mutation rate. It consists of 79 exons (0.6% of total gene) and codes for a 14 kb mRNA. The gene product is dystrophin, a 428 kd protein. It presents in the skeletal, cardiac and smooth muscles of the body and also in the brain. Deletion or duplication of gene segments is seen in two thirds of patients. Deletions are seen at two hot spots. Most common deleted region is between exons 43 and 52 followed by that between exons 2 and 21. Duplications are less common than deletions, and further smaller number of patients has point mutations, which require elaborate and expensive genetic testing (Cohn and Campbell 2000).

Duchenne muscular dystrophies (DMD) and Becker muscular dystrophy (BMD) are two allelic forms of single gene. Koenig explained its molecular basis by reading frame rule, which is applicable in 90% cases. Out-of-frame deletions lead to DMD, while in-frame deletions lead to BMD (Table 9.2). In the minority of patients who do not follow the frameshift rule, milder clinical phenotypes are seen, particularly in exons 3–7 (Koenig et al. 1988).

An example of a sentence is given. The first is considered as normal dystrophin (meaningful sentence), an out-of-frame mutation will result in abnormal molecule having no function (meaningless sentence) and in-frame mutation will result in partially effective dystrophin (sentence retains some meaning).

Dystrophin is located subsarcolemally and is a cytoskeletal protein (Fig. 9.3).

Absence of dystrophin has the following effects:

- Displacement of associated proteins
- Cytoskeletal abnormality
- Mechanical stress to membrane
- Change in membrane permeability
- Disrupt calcium homeostasis resultant excess cytosolic calcium
- Protease activation, for example, calpains

Table 9.2 Reading frame rule in DMD/BMD

The fat cat ate the rat	Normal dystrophin
The rat	DMD: out-of-frame mutation
The cat ate the rat	BMD: in-frame mutation

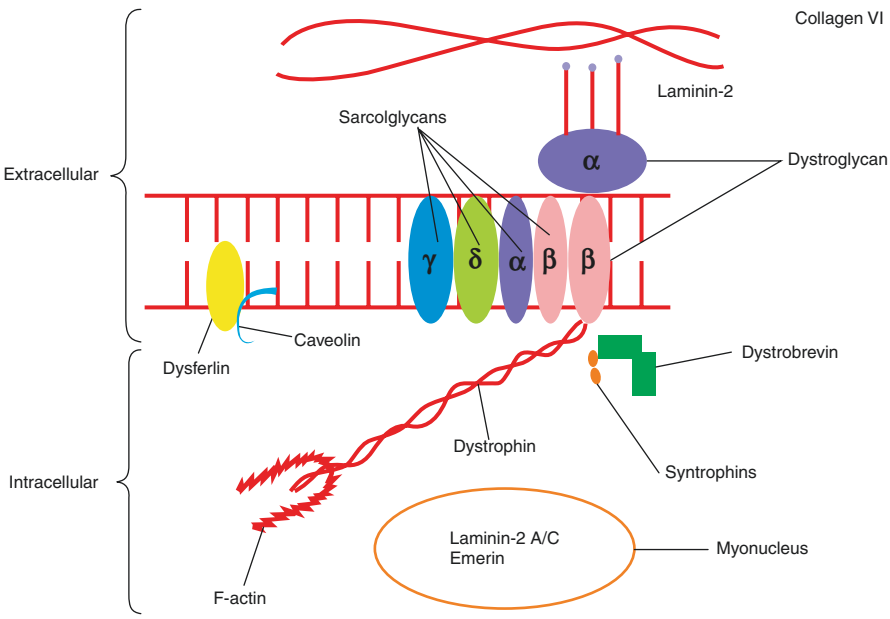

Fig. 9.3 Dystrophin–glycoprotein complex

Rando (2001)

Mdx mouse with nonsense mutation in exon 23 is a commonly studied animal model.

9.5 Investigations

First, determine the phenotype of the index case; examine the family members and estimate serum muscle enzymes.

9.5.1 Biochemistry

Serum CK levels are markedly elevated in patients with DMD. The elevations are often extreme, being in thousands. The CK is elevated at birth and tends to rise by 3 years of age. They progressively decrease as the child gets weaker and the muscle mass is lost. Serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) levels are also increased commensurate with the CK elevation. This is important to recognise, as often children are unnecessarily investigated for hepatic dysfunction.

9.5.2 Electrocardiography

Following ECG changes are known to occur in patients with dystrophinopathy secondary to structural changes in myocardium (posterobasal and lateral walls of left ventricle, spare right ventricle) and cardiac conducting system (Fig. 9.4):

- Sinus tachycardia
- Tall R1 in V1
- Prominent Q in I, aVL and V6 or in II, III and aVF
- Increased QT dispersion (Finsterer and Stöllberger 2003)

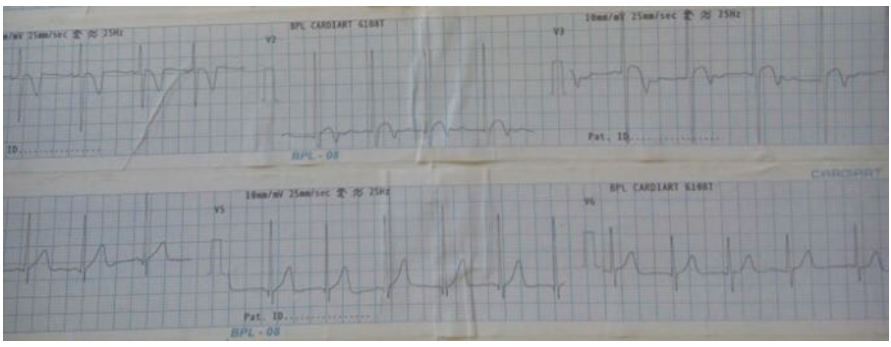

Fig. 9.4 Characteristic ECG changes in a patient with DMD

9.5.3 Genetic Evaluations

Genetic studies are important for accurate diagnosis, genetic counselling and prenatal diagnosis.

- Multiplex polymerase chain reaction (PCR):
  - Study 19–32 exons covering the hot spots.
  - Detect the common deletions.
- Multiplex ligation-dependent probe amplification (MLPA):
  - More sensitive technique for detecting deletions.
  - Study all the 79 exons.
  - Able to detect duplications.
  - Increase the yield by about 10%.
- Direct sequence analysis:
  - Not widely available
  - Expensive
- Targeted high-density oligonucleotide microarray technique:
  - Identify previously unidentified deep intronic mutations (Jones et al. 2003).

In India, multiplex PCR is regularly used in many centres in the research and service sectors, while MLPA is available in fewer set-ups. Carrier detection requires the MLPA test, as it studies the dosing effect. Prenatal genetic diagnosis requires chorionic villus sampling and is available in India (Dastur et al. 2008).

9.5.4 Electrophysiology

Normal nerve conduction study in early stages does not rule out diagnosis. Low amplitude compound muscle action potentials are noted in advanced cases. Needle EMG demonstrate myopathic potentials especially in proximal muscle groups. Some children have increased spontaneous activity which is believed to be due to reinnervation. As muscle mass reduces with advancement of the disease, motor units become progressively smaller and silent in some areas. Electrodiagnosis should be scheduled after collection of blood for CK level, as CK rises after needling of muscles. Also, it is preferable to avoid needle tests on muscles on which biopsy is planned (Manshukhani and Doshi 2008).

9.5.5 Imaging

Imaging helps to identify order, extent and degrees of muscle involvement. T1, T2, STIR and contrast studies are necessary for above objectives. Sequence of involvement in DMD is gluteus maximus and adductor magnus, quadriceps, rectus femoris and biceps femoris with relative sparing of other thigh muscles. In leg, gastrocnemii are more severely affected than other leg muscles (Chen et al. 2014).

9.5.6 Muscle Biopsy

Indication of biopsy in recent years is limited to situations where in clinical phenotype is atypical or genetic test is negative.

- Light microscopy:
  - Degenerating necrotic muscle fibres
  - Macrophage invasion
  - Regenerating muscle fibres clustering
  - Muscle fibre size variability
  - Fat and endomysial connective tissue deposition
- Histochemistry:
  - Type 1 fibre predominance
- Immunostain:
  - Absence of dystrophin

Three antibodies (Dys 1, 2 and 3) are available against dystrophin. They cover the carboxy terminus, central region and amino terminus. As each antibody covers only a portion of the protein, all three should be preferably used. In dystrophin deficiency as seen in BMD, the protein staining is irregular and fragmented (Voit et al. 1991). CK levels are raised in half of known carriers. MLPA can detect the carrier status.

9.6 Differential Diagnosis

The differential diagnosis of BMD is similar to that of LGMDs. Please refer to chapter on LGMDs for differential diagnosis and their key distinguishing features (Table 9.3).

Table 9.3 Differential diagnosis of DMD and BMD

Disease	Key differentiating features
Muscular dystrophies	
Emery–Dreifuss	Early elbow contractures, cardiac conduction defects
Facioscapulohumeral	Marked facial weakness, scapular winging
Limb–girdle	LGMD 2 C-F and I can have similar phenotype
Congenital	Early life dystrophy, may have MRI changes
Inflammatory myopathies	
Dermatomyositis	Skin rashes, Gottron's papules
Polymyositis	Non-selective weakness
Congenital myopathies	
Nemaline, centronuclear, central core disease	Early life weakness, normal CK, static course
Lipid storage disease (carnitine deficiency)	Exercise intolerance, myoglobinuria, biopsy changes
Glycogen storage disease (acid maltase deficiency)	Exercise intolerance, fixed weakness, biopsy changes
Mitochondrial myopathies	External ophthalmoplegia, short stature, cardiac changes, ragged red fibres

9.7 Management

9.7.1 General Management and Surveillance (Table 9.4)

Schools may not be sensitised to the needs of DMD children, and issues arising out of the special motor requirements of the child need to be individually addressed. Parental overprotection is common, and many children do not attend school, resorting to tuitions at home. Behaviour difficulties are common and counselling of the whole family unit can be beneficial.

9.7.2 Corticosteroid Therapy (Gloss et al. 2016)

The proposed mechanisms are changes in gene regulation, preventing muscle breakdown, lowering cytotoxic T cells, modifying calcium metabolism and improving muscle repair. Prednisolone/prednisone is usually given in the doses of 0.75 mg/kg/day. No or less benefit with low doses and no added advantage with high doses are noted. Various regimens like 1.25 and 2.5 mg/kg alternate day doses, 10 days on and 10 days off and 10 days on and 20 days off, followed by 5 mg/kg/dose twice weekly or 10 mg/kg/weekends have been followed. Deflazacort (0.9 mg/kg/day) can be used optionally.

Early corticosteroid treatment is beneficial but the optimal duration of the therapy is unclear. Results are seen within 10 days, peak at 3 months and sustained till 18 months. Side effects of corticosteroids should be monitored and treated timely. Prednisolone and deflazacort have similar efficacy but different side effect profiles. Equal efficiency of deflazacort and prednisone is established. Weight gain is more with prednisone while cataract is commoner with deflazacort. FOR-DMD trial is expected to give us clear idea about dose optimisation and therapeutic window of

Table 9.4 General management and surveillance in DMD

Cardiac	• Surveillance after 10 years of age • Annual ECG, 2D Echo; Holter (if rhythm disturbance present) • ACEI, beta blocker
Respiratory	• Surveillance before ambulation lost – annually; afterward – frequently • Polysomnography • Early management of respiratory infection • Vaccination – influenza, pneumococci • NIPPV – non-invasive positive pressure ventilation • Ventilatory support
Scoliosis	• Surveillance after 5 years of age • Surgery if degree of scoliosis is >25% and vital capacity >30% of predicted • Calcium and vitamin D supplement
Contracture	• Exercise program • Tendon release surgery

prednisolone versus deflazacort. In India, where prevalence of tuberculosis is high, corticosteroid treatment may flair up underlying tuberculosis. In a recent survey carried out in Asian–Oceanian countries, use of steroids was shown to vary from country to country.

9.7.3 Other Drugs

Histone deacetylase inhibitor: givinostat

Oxide-donating drugs (isosorbide dinitrate) with nonsteroidal anti-inflammatory drugs (NSAIDs): ibuprofen

Drugs like oxandrolone, azathioprine, cyclosporine, creatine monohydrate, nifedipine, leucine, selenium and vitamin E and antiserotonergic drugs methysergide and pizotifen have been tried in research settings, without robust evidence towards benefit.

9.7.4 Gene Therapy

The DMD gene is very large and, hence, it is difficult to have a viral vector to carry the entire gene. Critical fragments of the gene can be carried by adeno-associated viral vectors. Such microdystrophin and minidystrophin genes have been injected in mice, and dystrophin has been successfully expressed. How to provide the gene to multiple muscles groups is an issue as is the potential downsides of persistent immunomodulation amongst the recipients (Muntoni and Wells 2007).

Antisense oligonucleotide exon-skipping technique redirects splicing and produces functioning dystrophin. However, the antisense oligonucleotide has to be tailored to the deletion which is a limitation. Providing sustained therapy is another unanswered issue. Gentamicin and PTC 124 have been studied for altering stop codons. Gentamicin has not been successful in clinical trials. PTC124 (ataluren, Tranlsarna™) is an oral nonaminoglycoside drug. It has no antibiotic properties. The European Union grants ataluren use in ambulatory DMD patient above 5 years of age (Wilton and Fletcher 2008). Utrophin upregulator, SMT C1100 (2-arylbenzoxazole (5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo(d)oxazole)), is under trial and the results are awaited.

Myoblast transfer and bone marrow-derived stem cell transfer have been used in research settings. Mesenchymal stem cell sources presently appear most promising (Cossu and Sampaolesi 2007).

The most relevant part of the genetic advances is the ability to prevent the further occurrence of the disease in families. Genetic counselling plays important role. Important preventive step is identification and counselling of female carriers. Prenatal diagnosis should be pursued for carrier mothers and is most helpful when deletion is detected in the index case. Chorionic villus sample is tested for the DMD gene at 10–12 weeks of gestation, and affected conception is medically terminated. It is important to remember that germline mosaicism can go undetected when the carrier testing is performed. When mosaicism exists, the risk for future pregnancies is considered to be approximately 10–20%.

9.8 Prognosis

Death is usually the result of pulmonary infections and respiratory failure and sometimes of cardiac decompensation.

9.9 Case Study

Clinical details: A 10-year-old boy presented with complaints of cramps/muscle aches in both thighs and calves since 4 years of age. Pain increased on activity and got better with rest. Four months before presentation, he has noticed cramps in both shoulders. He had no history of limb weakness, getting up from sitting position, buckling of knees while walking or lifting arms overhead. But he tended to fall backwards on squatting. There was no bulbar weakness, respiratory symptoms or dark-coloured urine. Patient was born out of nonconsanguineous marriage, and there was no family history of any neuromuscular disease. On examination, there was no weakness, and he could get up from sitting position without any difficulty. Presence of calf hypertrophy was only the positive sign on examination (Fig. 9.5). Investigations revealed CK of 3400 IU and myopathic potentials on needle electrode examination (NEE).

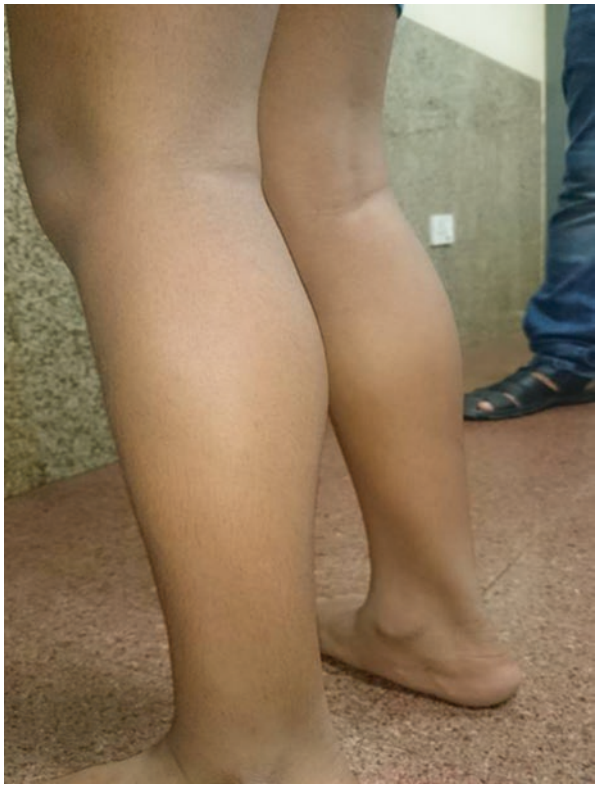

Fig. 9.5 Calf hypertrophy in a patient with cramp myalgia syndrome

Summary: Young boy presenting with cramps and myalgia, calf hypertrophy, minimal weakness, hyperCKaemia and myopathic potentials on NEE

Discussion: Various disorders which can present with early and prominent muscle cramps

- Myogenic disorders: dystrophinopathy, caveolinopathy, myotonia congenita, glycogen storage disorders and Brodie's disease
- Neurogenic disorders: neuromyotonia, amyotrophic lateral sclerosis and cramp fasciculation syndrome
- Systemic disorders: hypothyroidism, electrolyte imbalance, dehydration, pregnancy, stiff person syndrome, old age and medications

Diseases that can cause calf hypertrophy

- Dystrophinopathy
- Limb–girdle muscular dystrophies (sarcoglycanopathy, fukutin-related myopathies and caveolinopathy)
- Myotonic disorders (myotonia congenita and Schwartz–Jampel syndrome)
- Metabolic myopathies (hypothyroidism and Pompe's disease)
- Neuromyotonia
- Amyloidosis
- Sometimes, spinal muscular atrophy

Combination of calf hypertrophy, muscle cramps and myogenic potentials on NEE occurs in dystrophinopathy and hypothyroidism. Calcium, phosphorus, vitamin D and thyroid levels were within normal limits. Xp21 analysis showed deletions of exons 45 to 55, thus confirming dystrophinopathy. Cramp myalgia syndrome is a milder dystrophin phenotype, and patients present with calf hypertrophy, minimal weakness, cramps, hyperCKaemia and deletion of dystrophin gene. Commonly associated mutations of rod domains in exons 45–55 (most common) but mutations in exons 10–22 and 13–17 have also been described. Unlike other forms of dystrophinopathy, cramp myalgia syndrome has much milder disability and overall better prognosis.

Key Points

When to suspect

- Male child (X-linked recessive)
- Normal birth history
- Childhood-onset progressive proximal muscle weakness (Gower's sign)
- Pseudohypertrophy of muscles, especially calf
- Cardiomyopathy

How to investigate

- Serum creatine kinase
- EDX (particularly if inconclusive CK level)
- MRI
- Molecular genetic testing
- Muscle biopsy with immunostain for dystrophin (if genetic testing is not available or uninformative)

How to treat

- General supportive care
- Corticosteroids
- Potential gene therapy

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Spinal Muscular Atrophy

10

10.1 Introduction

Spinal muscular atrophy (SMA) is a group of genetic disorders which lead to degeneration of anterior horn cells and muscular weakness. They have a wider age of onset stretching from infancy to adulthood. Most of the cases are due to survival motor neuron (SMN) gene mutation. While mutations are seen in SMN 1 gene, the second gene, SMN 2, has a bearing on clinical severity, relating to number of its copies present in the affected individuals. Other non-SMN SMAs are uncommon, but are being increasingly recognised. Genetic identification has not been achieved for some of these, as yet. Current research focuses on the pathogenic aspects of these conditions, in order to move closer to definitive therapy. When a sporadic case is encountered, it becomes particularly important to differentiate SMA from its mimics. At present, there is no cure for this illness, but a sound knowledge of this group of disorders is necessary for the management, prognosis, genetic screening and prevention (Kolb and Kissel 2015; Darras 2015).

10.2 Epidemiology

SMA has been reported widely from Asian as well as Western world (Zerres and Rudnik-Schoneborn 1995; Finkel et al. 2014; Swoboda et al. 2005; Kaufmann et al. 2011). Among Asian countries genotype–phenotype correlation studies are available from China, Japan, Korea and Iran (Ni et al. 2015; Sedghi et al. 2014; Song et al. 2015; Hashizume et al. 2015). There is no particular sex predilection for SMA. As spinobulbar muscular atrophy (SBMA) is an X-linked disorder, it is manifested only in males. Initial studies from India demonstrated genotype–phenotype correlation in SMA (Dastur et al. 2006; Kesari et al. 2005). Small case series of genetically proven SMA have been reported from southern India (Swaminathan et al. 2008; Panigrahi et al. 2002).

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10.3 Clinical Features

10.3.1 SMA

The disease manifests as symmetric, predominantly proximal limb, trunk and neck weakness with involvement of cranial nerve nuclei. The presenting features of illness vary according to age of onset based on which, SMAs have been classified into its subtypes. Infants present with as 'floppy baby', children with delayed motor milestones and adolescents and adults with progressive weakness. International consortium on SMA has categorised phenotypes on the basis of age at onset, severity of illness and number of SMN2 repeats (Table 10.1).

10.3.1.1 SMA 0

It is the most severe form of SMA and is used to describe neonates with severe weakness, hypotonia and joint contractures. There is often history of decreased foetal movements, and patients usually have respiratory distress at birth, which is life-threatening. It is one of the causes of arthrogryposis multiplex. SMN 2 copies are severely reduced, and survival is up to 6 months (Kolb and Kissel 2015; Markowitz et al. 2012; Darras 2015; D'Amico et al. 2011).

10.3.1.2 SMA 1

It is also known as Werdnig–Hoffman disease. Patients with this subtype present within first 6 months with hypotonia and weakness. They have poor head control and never learn to sit. Baby assumes a characteristic posture at rest with thighs externally rotated and abducted with knees flexed known as the 'frog leg' posture. Deep tendon reflexes are absent. Fasciculation of tongue and fingers are often present. They also have associated bulbar and intercostal muscle weakness which poses a risk of aspiration and respiratory failure. These children fail to thrive and succumb to illness within 2 years. It is important to note that a number of lower motor neuron (LMN) disorders can present as a floppy baby (Kolb and Kissel 2015; Markowitz et al. 2012; Darras 2015; D'Amico et al. 2011).

Table 10.1 Features of different types of SMA

Type	Age of onset	Highest function achieved	Life span	SMN 2 repeats
0	Prenatal	Unable to reach motor milestones	Less than 6 months	1
1	0–6 months	Never sits supported	Less than 2 years	2
2	<18 months	Sits independently but cannot stand	70% live till 25 years of age	3, 4
3a	18 months to 3 years	Stand-alone	Almost normal	3, 4
3b	>3 years	Stand-alone	Almost normal	4
4	Second to third decade	Stand-alone	Normal	4–8

Kolb and Kissel (2015), Markowitz et al. (2012), Darras (2015), D'Amico et al. (2011)

10.3.1.3 SMA 2 (Dubowitz)

These patients present between 6 and 18 months. Motor developmental milestones are delayed. Children learn to sit without support but cannot stand on their own. Apart from hypotonia, weakness and areflexia, they have joint contractures, high arched palate, chest wall deformity, scoliosis and respiratory weakness. Cognition is normal. These patients survive up to childhood and adolescence (Sedghi et al. 2014).

10.3.1.4 SMA 3

It is also known as Kugelberg–Welander disease. These patients achieve their motor milestones and are able to stand without support at some point. Subsequently, they present with progressive weakness of proximal lower limbs than upper limbs. Illness leaves patients wheelchair bound, but they continue to survive as respiratory muscles tend to function better unlike other SMA subtypes (Kolb and Kissel 2015; Markowitz et al. 2012; Darras 2015; D'Amico et al. 2011).

10.3.1.5 SMA 4

This form is also known as pseudo-myopathic SMA. It presents with progressive proximal lower and upper limbs weakness. As this subtype has maximum number of SMN2 repeats, deficits are usually mild and patients remain ambulatory till late. Many experts suggest that age of onset more than 30 years should be considered for SMA 4 (Piepers et al. 2008).

The group described above, the SMN gene-related SMAs, accounts for majority of SMAs. The remaining (non-SMN SMAs) comprise of heterogeneous conditions, which are transmitted as recessive, dominant and X linked or are sporadic (Table 10.2).

10.3.2 X-linked Spinobulbar Muscular Atrophy (SBMA)

SBMA or Kennedy's disease is an X-linked CAG repeat disorder of the gene encoding for androgen receptor. The average age of onset is in 40s and 50s, but younger onset of SBMA has been reported (Fratta et al. 2014; Chahin et al. 2008; Querin et al. 2016; Rhodes et al. 2009). Most patients present with lower limb weakness, but few patients can have onset in upper limbs. Rarely, illness can begin in bulbar muscles. At the onset of illness, weakness can be asymmetrical in more than 50% of cases (Fratta et al. 2014; Rhodes et al. 2009). Limb weakness occurs both proximally as well as distally (Rhodes et al. 2009). Although weakness is the most common presenting complaint, tremors precede onset of weakness by a decade (Fratta et al. 2014). Apart from tremor and limb weakness, other features include dysarthria, dysphagia, tongue and facial fasciculations, sexual dysfunction, gynaecomastia, sensory symptoms and muscle cramps. Deep tendon reflexes are depressed or absent but can be normal (Udd et al. 1998). There are associated endocrine abnormalities in the form of androgen insensitivity and glucose intolerance. Absence of

Table 10.2 Features of non-SMN SMAs

Disease	Gene	Phenotype	Inheritance pattern
Spinal muscular atrophy with respiratory distress (SMARD)	IGHMBP2	Hypotonia, respiratory distress and cardiomyopathy	Autosomal recessive
Distal SMAs	GARS, dynactin 1, SLCA 7	Distal limb weakness, vocal cord paralysis	Autosomal dominant, autosomal recessive
Late-onset SMA	Vesicle-trafficking protein (VAPB)	Limb–girdle weakness	Autosomal dominant
Hereditary motor neuropathy 8	TRPV 4 mutation	Congenital, nonprogressive, weakness only localised to lower limbs	Autosomal dominant
SMA with lower extremity predominance (SMA-LED)	Dynein gene mutation	Early childhood-onset weakness and wasting of limbs with contractures	Autosomal dominant
Pontocerebellar hypoplasia with SMA	(Vaccinia-related kinase 1)VRK 1 and EXOCS3	Early-onset weakness, cerebellar ataxia, arthrogryposis and poor survival	Autosomal recessive
Non-SMN1 SMA	Neuronal apoptosis inhibitory protein (NIAP)	Found in Iran and Tunisia	Unknown
X-linked bulbospinal muscular atrophy	CAG trinucleotide repeats	Bulbar, distal > proximal limb, weakness and tremors	X-linked recessive

Darras (2015), Sedghi et al. (2014), http://neuromuscular.wustl.edu/synmot.html

upper motor neuron signs helps to differentiate from amyotrophic lateral sclerosis (ALS). Weakness is slowly progressive, and over decades, patients require supportive therapy for ambulation and feeding.

10.4 Pathophysiology

10.4.1 Genetics of SMA

SMA is caused by genetic mutations in survival motor neuron (SMN) gene located on chromosome 5. Majority of cases of SMA are due to SMN gene mutation. SMN is present in all tissues and is best expressed in motor neurons. It is important for RNA processing functions in all cells. SMN is coded by two genes: majority by SMN 1 and small proportion by SMN 2. SMN 2 is almost identical to SMN 1 except that SMN 2 lacks exon 7. Thus, SMN 2 is able to produce only a small proportion of functional protein. When mutation occurs in the SMN 1 gene, neurons rely on SMN 2 gene for production of SMN protein. Hence, more the number of SMN 2

copies, lesser is the severity of illness. In keeping with this, SMN 2 copies are maximum in number in adult-onset cases and least when onset is at birth. SMN is ubiquitous in expression, but its dysfunction leads only to anterior horn cell disorder. Remaining 5% of cases may be sporadic or caused by mutation in other genes, e.g. vesicle-trafficking protein (VAPB).

10.4.2 Genetics of SBMA

This is a trinucleotide repeat disorder characterised by expansion of CAG repeats in the first exon of androgen receptor gene. Repeats more than 38 in number are considered diagnostic. As in other repeat disorder, age of onset is inversely proportional to the number of repeats. SBMA patients with longer CAG repeats in range of 52–68 tend to have juvenile onset and severe weakness (Jokela and Udd 2016). Due to this mutation, motor neurons, sensory neurons and endocrine system are predominantly affected (Chahin et al. 2008).

10.4.3 Mutations in Genes Other than SMN 1

Apart from SMN 1 gene mutation which constitutes the majority of patients, few patients exhibit mutations in other genes. Mutations in VAPB, TRPV 4 and NIAP genes have been found in adult-onset cases. Rarely, mutations are detected in dynein, IGHMBP2, VRK 1 and EXOCS 3 genes (refer Table 10.2).

10.5 Investigations

10.5.1 SMA

Serum creatine kinase (CK) levels may be elevated two to four times of normal but is less than tenfold (Darras et al. 2014). Electrophysiology shows normal sensory conduction studies and decreased motor amplitudes. Needle electrode examination (NEE) shows changes of denervation and reinnervation in SMA 2 and 3, but such changes may be absent in early-onset cases. Muscle biopsy shows grouped atrophy and angulated fibres. Detection of homozygous deletion of exon 7 in both alleles of SMN 1 gene by polymerase chain reaction (PCR) is diagnostic of SMA (95–98% cases). Heterozygous mutation involving deletion in one exon 7 and point mutation in other allele can be found in 2–5% of patients (Markowitz et al. 2012).

10.5.2 X-linked SBMA

CK elevation tends to be more pronounced that one would expect for a neurogenic disorder. CK levels are elevated up to 1000 IU and highest value reported is 4300 IU

(Jokela and Udd 2016). Elevated glucose levels and deranged lipid profiles have been seen in a proportion of patients. Blood testosterone levels are significantly elevated in patients as compared to controls (Querin et al. 2016). NEE shows active and chronic denervation confirming LMN involvement. Yang et al. found that more than 50% of patients with SBMA had associated sensory neuropathy (Ni et al. 2015). Detection of CAG repeats more than 38 in the androgen receptor gene confirms the diagnosis (Fratta et al. 2014).

10.6 Differential Diagnosis

10.6.1 Early-Onset SMA

The main clinical manifestations of early-onset SMA are hypotonia, floppiness and abnormal motor milestones. The differential diagnosis is wide as floppy baby can be the result of a number of disorders, both central and neuromuscular. A higher proportion of patients having hypotonia in infancy have central cause (Peredo and Hannibal 2009). Hence it is important to ascertain whether hypotonia is coming from cerebral causes and when it is not so, to localise within the neuromuscular axis. Important features of central and peripheral causes of hypotonia are tabulated below (Table 10.3). In a minority of situations, both central and peripheral dysfunctions may coexist, e.g. aspiration leading to secondary hypoxic changes in a patient of SMA.

However, following points can help the localisation within different components of neuromuscular axis, i.e. neuron, nerve, muscle and neuromuscular origin (Table 10.4).

Table 10.3 Differentiation between hypotonia of central and peripheral origin

Features	Hypotonia of central (cerebral) origin	Hypotonia of peripheral (neuromuscular) origin
Features of encephalopathy, e.g. irritability, poor feeding, inability to spend some time of the day with eyes open	More common	Less common
Power checked by checking reflex movements to a noxious stimuli	Relatively preserved	More affected
Presence of fisting, i.e. holding thumb in closed hands	More common	Less common
Deep tendon reflexes	Normal or exaggerated	Depressed or absent
Primitive reflexes, e.g. moro and tonic neck reflex	Abnormal persistence or asymmetrical	Normal or depressed
Skeletal deformity like high arched palate, micrognathia, chest wall abnormalities, contractures, etc.	Less common	More common
Other organ malformations	More common	Less common

Table 10.4 Differential diagnosis of hypotonia of neuromuscular origin

Diseases	Key differentiating features
Congenital myotonic dystrophy	H/o polyhydramnios, prolonged labour, characteristic facial appearance with tenting of upper lips, thin cheeks and wasting of temporalis, facial diplegia. EMG shows myotonic discharges
Congenital myasthenic syndrome	Ptosis, ophthalmoparesis, episodes of weakness, apnoea and bulbar dysfunction; fluctuating course of illness with intermittent improvement; presence of positive family history; nerve conduction studies show decrement or repetitive discharges
Infantile Pompe's disease	Hypotonia without atrophy, enlarged tongue, organomegaly and cardiomyopathy. Lowered acid maltase activity in dried blood spot is diagnostic
Infantile botulism	Progressive bulbar and limb weakness, ptosis, ophthalmoparesis, poor light reflex, expressionless face and constipation
Benign congenital hypotonia	Diagnosis of exclusion. Symmetrical flaccidity, normal reflexes, hypermobile joints. There is delay in achieving motor milestones which they eventually acquire, but some cognitive deficits may be residual
Congenital myopathies	Centronuclear and nemaline myopathies have ptosis, extraocular and facial weakness. Nemaline myopathy has thin and long facies with neck drop. Features on muscle biopsy are characteristic for these congenital myopathies
Congenital muscular dystrophies	Infants with weakness, contractures, highly elevated CK, cognitive abnormalities and MRI brain shows white matter changes

Peredo and Hannibal (2009), Hebert et al. (2015), Prasad and Prasad (2011)

10.6.2 Adult-Onset SMA

These patients present with progressive proximal weakness. Closest differential diagnosis is muscular dystrophy (refer case), but a number of other anterior horn cell disorders and diseases due to nerve, muscle and neuromuscular dysfunction can mimic SMA. Close differentials with their key distinguishing features are mentioned below (Table 10.5).

10.7 Management

At present, there is no definitive therapy for SMA, but a comprehensive rehabilitation care can be given to reduce the disability. Various clinical trials have explored possible solutions for this illness.

10.7.1 Antisense Oligonucleotides (ASO)

These are RNA molecules that produce alteration of splicing and include exon 7 in SMN 2, thus generating full-length SMN mature RNA. In animal studies, median survival drastically increased with ASO administration, and this method

Table 10.5 Differential diagnosis of adult-onset SMA

Diseases	Key differentiating features
Progressive muscular atrophy	Male predominant, distal > proximal, asymmetrical weakness and wasting, prominent changes of ongoing denervation on EMG. Rapid progression as compared to SMA and mean survival is 56 months due to bulbar and respiratory involvement
X-linked spinobulbar muscular atrophy	Bulbar onset, perioral fasciculation, distal > proximal weakness, features of androgen resistance like gynaecomastia and associated sensory neuropathy. CK levels are elevated. Elevated CAG trinucleotide repeats are diagnostic
Polymyositis	Subacute onset, painful, female sex predominant, proximal weakness out of proportion of wasting and without any fasciculation
Chronic immune demyelinating neuropathy	Associated sensory involvement, areflexia, no wasting or fasciculation, thickened nerves, elevated CSF protein and NCS shows widespread demyelination
Myasthenic syndromes (cases with prominent limb weakness without extraocular involvement, e.g. DOK-7 mutation)	First to second decade onset, weakness and wasting, no fasciculation, depressed reflexes, prominent day–night fluctuations, fatigability and RNS shows decrement response

can prove to be a potential disease modifier in the future (Zanetta et al. 2014). Nusinersen, which is a modified ASO, has been recently approved by US-FDA for treatment of SMA.

10.7.2 Molecules that Increase SMN 2 Expression

- Histone deacetylase inhibitors (HDACI): Histone deacetylase inhibitors play an important role in epigenetics of gene expression. Various HDACI like phenylbutyrate and valproic acid have been studied. HDACI have been found to increase SMN 2 levels, but this has not been translated into clinical improvement in SMA (Kissel et al. 2014; Darras 2015).
- Hydroxyurea: It enhances expression of SMN 2 in SMA patients through nitric acid release. Randomised controlled trial failed to show any clinical improvement in SMA patients (Xu et al. 2011; Chen et al. 2010).
- Salbutamol: In a pilot study, salbutamol was found to be well tolerated but had no significant improvement in functions of SMA 2 (Pane et al. 2008).

10.7.3 Neuroprotective Agents

- Riluzole: Despite its inhibitory effects on glutamate and ability to alter excitotoxicity, riluzole has not been found to promote recovery of lost motor neurons or show any improvement in motor function at the end of 6 months (Calder et al. 2016).

- Ceftriaxone: In animal trials, ceftriaxone has shown to increase survival time and slightly improved motor function, but further evidence is awaited (Nizzardo et al. 2011).
- Olesoxime: It is considered a novel neurotherapeutic agent, and trial is currently underway to detect its efficacy in SMA patient aged between 3 and 25 (Lloyd and Hunter 2011).

10.7.4 Gene Therapy

It aims to restore normal SMN 1 gene. In preclinical studies, gene therapy has given promising results which can hopefully be translated in human trials as well (Zanetta et al. 2014).

10.7.5 Supportive Care

It has been observed that resistance strength training tend to improve strength and motor functions and were well tolerated (Lewelt et al. 2015). Patients with SMA 1 and 2 have associated chest wall deformities and respiratory muscle weakness. Judicious use of non-invasive ventilatory support has shown to be helpful. Laparoscopic gastrostomy leads to improve nutritional status and prevent risk of aspiration in early-onset cases. Scoliosis and contractures can be dealt with orthosis and possibly surgical intervention in some patients (Darras 2015).

10.7.6 Prenatal Screening

In this incurable disease, prenatal screening assumes importance to prevent new sufferers from being born, by detecting the presence of mutation, predict severity of illness and help parents to tailor their responses accordingly (Burns et al. 2016).

10.8 Prognosis

The severity of SMA depends on number of SMN 2 repeats. SMA 1 and 2 have lesser number of repeats and thus have severe illness, respiratory muscle weakness and poor survival rates. SMA 3 and 4 have near-normal survival but may become non-ambulatory as disease progresses. X-linked SBMA is slowly progressive and renders patient wheelchair bound as it progresses.

10.9 Case Study

Clinical details: A 17-year-old male presented with slowly progressive proximal weakness of lower limbs, 9 years before presentation. He required support to get up from sitting position and was managing to walk without any external support. He

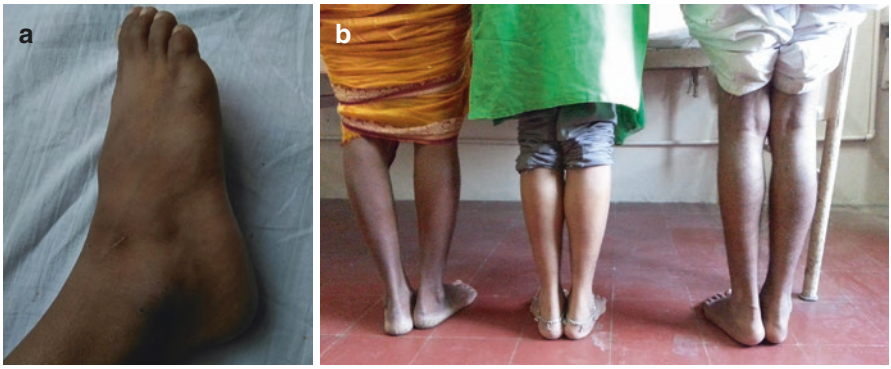

Fig. 10.1 (**a**) Prominent EDB and (**b**) mother (*left*) having normal calves, while two siblings have mild enlargement of calf muscles

noticed thinning of muscle bulk over thighs and arms gradually over years. He also noticed tremulousness of hands while holding cup of water and writing. He was born of consanguineous marriage (parents were third cousins), and out of other two siblings, one sister was affected. This affected sister had milder weakness since 10 years of age and could get up from sitting position on her own. Mother had noticed that calves of both siblings were prominent. On examination, proximal power in lower limbs was grade 3/5 and was normal distally. Proximal power in upper limbs was grade 4/5. Both calves and extensor digitorum brevis (EDB) muscle looked prominent as compared to other muscles (Fig. 10.1). All deep tendon reflexes were normal. Ankle contractures were present. Outstretched hands showed involuntary movements of fingers which were rapid, jerky and irregular. No fasciculations were seen. He had no cardiac or respiratory complaints or any fluctuations in course of his illness.

Summary: This 17-year-old male had a familial, slowly progressive, proximal, predominantly lower limb weakness and wasting, prominent calves, well-seen EDB muscles and irregular tremors of outstretched hands.

Discussion: Based on this clinical picture, two differentials were thought of: (1) muscular dystrophy and (2) spinal muscular atrophy. The following points help to differentiate between these two conditions (Table 10.6).

Patient was investigated. ECG and CK levels were normal. EMG showed features of chronic denervation. Nerve conduction parameters were normal. Genetic evaluation showed deletion in exons 7 and 8 of SMN gene consistent with diagnosis of SMA. This case highlights the overlap of the clinical points made in the above table. It is important to appreciate that these differences are not absolute, e.g. asymmetry can occur in muscle diseases, prominent calves and EDB can occur in SMA and depressed deep tendon reflexes may be seen in muscle diseases. In interpreting various clinical findings, care has to be exercised in prioritising the site of localisation.

Table 10.6 Differentiating SMA from muscular dystrophies

Spinal muscular atrophy	Muscular dystrophy
Wasting is out of proportion to weakness	Weakness is out of proportion to wasting
Fasciculation can be seen	Fasciculation is absent
Differential weakness amongst different muscles of a joint is usually absent	Differential weakness is often present, e.g. hip adductors more weak than abductors in limb–girdle muscular dystrophy
Deep tendon reflexes are depressed to absent even in muscles that show normal power	Deep tendon reflexes are usually preserved
Muscle hypertrophy is usually absent	Muscle hypertrophy or pseudohypertrophy usually suggests muscular dystrophy
Fasciculatory tremors of upper limbs are characteristic of neurogenic disorder	Such tremors are absent in muscular dystrophy Presence of tremors in a case of proximal weakness makes muscular dystrophy very unlikely
Neck and bulbar weakness more common	Neck and bulbar involvement less common
Asymmetrical involvement more common	Less common and can occur in few muscle diseases, e.g. anoctaminopathy, facioscapulohumeral dystrophy
Family history: autosomal recessive inheritance pattern	Autosomal recessive or X-linked pattern seen
Creatine kinase mildly elevated	Creatine kinase levels often moderately or severely elevated
ECG is normal, and there is no evidence of cardiomyopathy	Muscular dystrophies can be accompanied by cardiomyopathy and ECG changes, e.g. dystrophinopathy
EMG shows features of chronic and sometimes active denervation	EMG shows myopathic potentials

Key Points

Spinal muscular atrophy
When to suspect

- Early life presentation with progressive weakness and wasting
- Diaphragmatic and bulbar involvement
- Normal sensations
- Familial nature

How to investigate

- Modest CK elevation
- Electrophysiology showing widespread de- and reinnervation
- SMN 1 gene deletion (exon 7 or 8)

How to treat

- Symptomatic and supportive
- Nusinersen

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Idiopathic Inflammatory Myopathies 11

11.1 Introduction

The IIMs are diverse group of disorders having following common features.

- Onset is acute, subacute or chronic.
- Distribution is proximal and symmetrical (except IBM).
- Elevated CK (creatine kinase).
- EMG shows irritative muscle disease.
- Muscle biopsy reveals inflammatory exudates.

When inflammatory myopathies are associated with connective tissue disease like SLE or scleroderma, they are known as overlap syndrome (OS) (Dimachkie and Barohn 2012). Interstitial lung disease may be associated with juvenile dermatomyositis (JDM) along with Jo-1 antibodies (Hochberg et al. 1984; Van der Meulen et al. 2003; Marie et al. 2011). Malignancy are commonly seen with DM followed by PM and NM (Chen et al. 2010; Miller T et al. 2002; Miller J et al. 2002).

Dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM), necrotising myopathies (NM), eosinophilic, granulomatous and drug-induced myopathies are discussed in this chapter.

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11.2 Epidemiology

Incidence rates: 2–8 per million
Prevalence rates: 10–63 per million
Cronin and Plotz (1990), Oddis et al. (1990), Patrick et al. (1999)

11.3 Clinical Features

The common clinical denominator is the rapidly evolving, symmetric, proximal muscle weakness often with dysphagia and neck weakness. Apart from this, some clinical clues exist in various forms of IIMs, which are tabulated below (Table 11.1).

Table 11.1 Clinical features of various IIMs

Diagnosis	Salient clinical features
Dermatomyositis	Age of onset: 10–40 years of age Disease onset: Acute or insidious Weakness: Proximal and painless Skin manifestations: Heliotrope rash, Gottron's papules (Fig. 11.1), V-sign and Shawl sign (Quinter et al. 2012), subcutaneous calcification, pruritus (Schmeling et al. 2011; Shirani et al. 2004; Hundley et al. 2006; Medsger and Oddis 1995) Polyarthritis (Tymms and Webb 1985) Two types: 1. Isolated skin manifestation is known as amyopathic DM 2. Isolated muscle involvement is known as adermatopathic DM
Antisynthetase syndrome	Mechanic's hands, arthritis, Raynaud's phenomenon, interstitial lung disease
Polymyositis	Age of onset: Over 20 years of age Disease onset: Subacute or insidious Weakness: Proximal and symmetrical (Bohan and Peter 1975) Dysphagia (1/3rd patients), jaw-opening weakness in few patients (Pal and Sanyal 2011)
Cervicobrachial polymyositis	Neck and shoulder weakness, finger extensor weakness, respiratory weakness (Khadilkar et al. 2014)
Inclusion body myositis	Age of onset: After 50 years age Weakness: Distal and asymmetric – deltoids, quadriceps, forearm muscles, ankle dorsiflexors Course: Indolent and treatment refractory (Cohen et al. 1989) Additional neuropathy may occur (Leff et al. 1993)
Necrotizing myopathy (NM)	Onset: Subacute Clinical features: Progressive and proximal (Van der Meulen et al. 2003), myalgia, dysphagia Associations: Malignancy esp. adenocarcinoma Necrotizing myopathy with pipestem capillaries: Weakness, vasculitis, or connective tissue disease Brain infarction may occur Signal recognition particle (SRP) autoantibodies: Earlier age, fulminant course, heart-related complications (Suzuki et al. 2011)

Table 11.1 (continued)

Diagnosis	Salient clinical features
Statin-associated inflammatory myopathy	Autoimmune NM, also known as statin-induced autoimmune NM (SANAM) Occurs in susceptible individuals May progress after drug has been stopped May occur several years after drug had been stopped Require immunosuppressive treatment (Grable-Esposito et al. 2010)
Eosinophilic myositis and fasciitis	Similar to PM Systemic hypereosinophilic syndrome (haematological, dermatological, respiratory, cardiac and nervous system manifestation) (Pickering and Walport 1998) Shulman's syndrome (Eosinophilic fasciitis) (Shulman 1975) Eosinophilic perimyositis Eosinophilia–myalgia syndrome
Granulomatous myopathy	Rare Associations: Systemic sarcoidosis, IBM, Wegener's granulomatosis, rheumatoid disease, myocarditis, biliary cirrhosis and Crohn's disease, thymoma and thyroiditis, myasthenia gravis, pancytopenia (Mozaffar et al. 1998; Danon et al. 1986; Drachman 1963; Hermann et al. 2000; Menard et al. 1976)
Aluminium hydroxide-containing vaccines	Muscle pain and weakness, joint pain, fever Raised erythrocyte sedimentation rate Periodic acid–Schiff (PAS)-positive macrophages and lymphocytes infiltration in endomysium and perimysium (Gherardi et al. 1998, 2001)

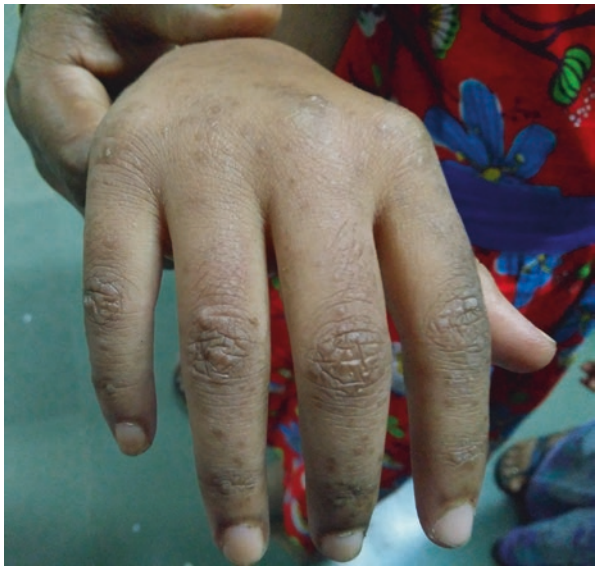

Fig. 11.1 Gottron's papules in a patient with dermatomyositis

11.4 Pathophysiology

DM:

- Complement-dependent humoral process.
- Antibodies to endothelial cells cause microangiopathy that leads to secondary ischaemic changes in muscles.

PM and IBM:

- T-cell response
- Muscle fibre invasion by CD8+ lymphocytes
- Perforin-mediated cytotoxic necrosis

IBM:

- Autophagia with rimmed vacuole formation and inclusions containing β-amyloid and other proteins
- Proteasomal dysfunction

11.5 Investigations

The key investigative findings are tabulated in Table 11.2.

11.5.1 Muscle Biopsy

- Selection of muscle:
  - Moderately weak muscle
  - Muscle showing active inflammation on MRI
  - Muscle that is not needled during EMG
- Preferred muscles:
  - Biceps brachii, vastus lateralis, deltoid
- Method
  - Open biopsy – advantage of enough tissue sample, less sampling error
  - Needle biopsy – less preferred method

Table 11.2 Key investigations in IIM

Investigation	Salient features
Serum creatine kinase	Increased in the majority of DM patients, normal in 10% Always elevated in active PM (5–50 times) Less striking elevation in IBM, normal in 20–30% Decrease generally correlates with therapeutic response
Electromyography	Spontaneous activities: Significant and suggest active disease Motor Unit Potentials (MUPs): Early recruitment, small amplitude, short duration IBM: Additional evidence of neuropathy (Dabby et al. 2001) SANAM: Electrical myotonia Electromyography is helpful in differentiating relapse from corticosteroid myopathy
Muscle biopsy dermatomyositis Polymyositis Inclusion body myositis	• Perifascicular muscle fibre atrophy (specific finding), focal inflammatory cells infiltrates, predominant CD4-positive T cells (Fig. 11.2) • Perimysial and perivascular inflammation, focal, scattered muscle fibre necrosis, predominant CD8-T-positive cells • Endomysial inflammation, muscle fibre hypertrophy, less commonly muscle fibre atrophy confused with denervation, mainly CD8+ T cells and some macrophages, rimmed vacuoles with granular material and filaments measuring 15–18 nm, composed of b-amyloid, desmin, ubiquitin, etc. (Mastaglia et al. 2003)
Screening for malignancy	Dermatological examination for melanoma Examination of pelvic, testis and prostate Stool for occult blood Colonoscopy after age of 50 Computed tomography (CT) scan of the chest, abdomen and pelvis Screening should be done at every 3–6 months (Titulaer et al. 2011)
Interstitial lung disease (ILD)	Pulmonary function test (PFT) Chest CT scan Jo-1 (histidyl t-RNA synthetase) antibody (Hochberg et al. 1984) Biomarkers for activity and severity monitoring: Serum KL-6, SP-D, IL-18,ferritin (Fathi et al. 2012; Gono et al. 2010)
MRI imaging	Active inflammation: Enhancement of muscle tissue on T2-weighted images (but not T1-weighted images) Fatty infiltration: Enhancement of both T1- and T2-weighted images MRI with short tau inversion recovery (STIR) images: Differentiate oedema fatty infiltration (Degardin et al. 2010; Reimers et al. 1994)
CT scan of muscle	To detect calcification in DM

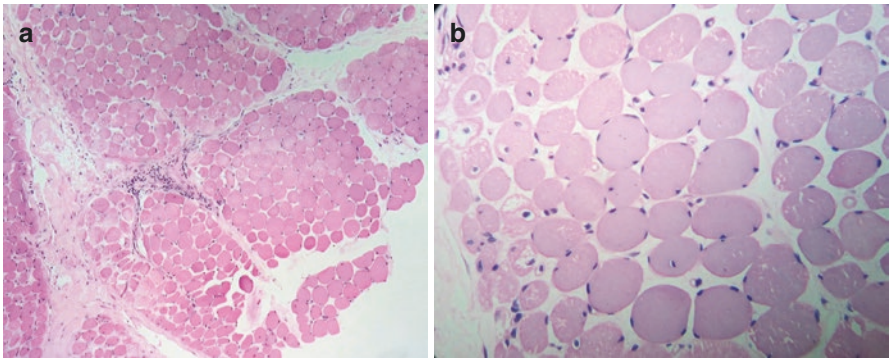

Fig. 11.2 (**a**) HE (10X): Muscle tissue with perivascular inflammatory infiltrate and (**b**) HE (40X): Muscle tissue with perifascicular atrophy in DM

- Time:
  - Usually before start of treatment
- Analysis:
  - Light microscopy
  - Immunohistochemical study: Look for T-cell type, HLA class antigen, amyloid, ubiquitin, SMI 31
  - Electron microscopy: Tubuloreticular endothelial cell inclusion (DM), tubulofilamentous inclusion (IBM)
- Advantage of biopsy over other methods of diagnosis:
  - Provide definite diagnosis
  - Identify types of muscle inflammation
  - Judge severity of myositis
  - Gives clue to aetiology like parasitic, granulomatous
- Disadvantages:
  - Diagnosis can be missed because of the patchy nature of the process and rimmed vacuoles may not be present early in disease

11.5.2 Antibody Studies (Table 11.3)

Inflammatory myopathies show antibodies to nuclear or cytoplasmic constituents. Antibodies seen only in patients with inflammatory myopathies are known as

Table 11.3 Pathogenic antibodies, clinical manifestations and syndromes of IIMs

Syndrome	Antibodies	Salient clinical features
Autoimmune necrotizing myopathy	Anti-SRP	Subacute severe myopathy; refractory to treatment
	Anti-HMGCR	Subacute myopathy ± statins
Dermatomyositis	Anti-Mi2	Classic DM; lesser systemic involvement; good prognosis
	Anti-SAE	CADM; associated gastrointestinal features and more systemic involvement
	Anti-TIF1	Severe cutaneous features; associated with malignancy
	Anti-NXP2	Similar to TIF1; calcinosis and contractures can be seen
Myopathy with pulmonary involvement		
ASS	Anti-ARS	ILD; CADM; mechanic's hands; Gottron's lesion; Raynaud's phenomenon; inflammatory arthritis
Dermatopulmonary	Anti-MDA5	
	Anti-PMScl	
Overlap CTD–SSc–myopathy	Anti-PmScl	ILD; diffuse skin disease; PAH; gastrointestinal manifestations
	Anti-U3RNP	
	Anti-RuvBL1/2	

ASS anti-synthetase syndrome, *MDA5* melanoma differentiation gene 5, *SRP* signal recognition particle, *HMGCR* hydroxy-3-methylglutaryl-coenzyme A reductase, *SAE* small ubiquitin-like modifier activating enzyme, *TIF1* transcriptional intermediary factor 1, *NXP2* nuclear matrix protein 2, *ILD* interstitial lung disease, *CADM* clinically amyopathic dermatomyositis, *U3RNP* U3-ribonucleoprotein, *RuvBL1/2* nuclear/nucleolar matrix complex.
Anti-ARS (acetyl-tRNA synthetases): Anti-Jo1, anti-PL12, anti-PL7, anti-OJ, anti-EJ, anti-KS, anti-Ha, anti-Zo (Gunawardena 2017; Benveniste et al. 2011)

myositis-specific antibodies, while antibodies additionally seen in other connective tissue diseases are known as myositis-associated antibodies.

11.6 Differential Diagnosis

Presentation with muscle pain and weakness opens differential diagnosis of inflammatory myopathies. It could be infectious, endocrine related, metabolic muscle disease, neurological, fibromyalgia, polymyalgia rheumatica, sarcoid or paraneoplastic (Table 11.4).

Table 11.4 Differential diagnosis and key differentiating features in IIM

Group of diseases	Key differentiating features
Drug or toxins	
Amiodarone, chloroquine, cimetidine, clofibrate, cocaine, colchicine, corticosteroids, danazol, emetine, ethanol, gemfibrozil, heroin, HMG-CoA reductase inhibitors (statins), hydralazine, ipecac, ketoconazole, levodopa, nicotinic acid, penicillamine, phenytoin, procainamide, rifampin, sulfonamides, vincristine, zidovudine	History of exposure Chronic, progressive, symmetrical, proximal weakness Coasting (symptoms continue to worsen after exposure) Some are associated with a n axonal neuropathy
Infection	
Bacterial (staphylococcal, streptococcal, pneumococcal, salmonella) Treponemal (syphilis) Mycobacterial (*Mycobacterium tuberculosis*, *M. leprae*) Viral (CMV, EBV, HIV, HSV, adenoviruses, others) Fungal (cryptococcosis, mucormycosis), parasitic (trichinosis, toxoplasmosis)	Constitutional features, exanthematous rashes, myopathy is a part of multiorgan involvement, subcutaneous oedema, pain tenderness of muscles
Metabolic myopathies	
Glycogen storage diseases, carnitine deficiency, carnitine palmitoyltransferase deficiency	Exercise intolerance Second wind phenomenon
Endocrinopathies	
Hypothyroidism, hyperthyroidism, hyperparathyroidism, Cushing syndrome, vitamin D deficiency	Systemic features of the endocrinopathy Myopathy as part of a larger syndrome
Neuromuscular disorders	
Amyotrophic lateral sclerosis, muscular dystrophy, myasthenia gravis	ALS: UMN and LMN features Muscular dystrophies: A clinically oriented scoring system (Khadilkar et al. 2008)
Polymyalgia rheumatica	Elevated ESR, severe muscle pains without weakness
Fibromyalgia	Tender points on examination of muscles
Sarcoidosis	Lymphadenopathy, bifacial weakness, neuropathy, elevated ACE levels, Gallium scan abnormalities

11.7 Management

11.7.1 Corticosteroids

Regime:

- Induction:
  - Prednisone 1 mg/kg/d (60–100 mg) for 4 weeks.
  - Lower dose 0.5 mg/kg/day in diabetic, hypertensive and osteoporotic patients reduce side effects.

  - Nzeusseu shows similar efficacy of high (>0.5 mg/kg) and low (<0.5 mg/kg) doses of prednisolone (Nzeusseu et al. 1999).
- Indication of intravenous methylprednisolone:
  - Severe weakness, extramuscular involvement like ILD, gastrointestinal angiopathy (Genge and Karpati 1997; Matsubara et al. 1994).
  - Pulse dexamethasone is also effective (Van der Meulen et al. 2000).
- Maintenance:
  - Standard tapering schedule: 60–100 mg every other day or its equivalent dose for first few months. Once patients respond well, taper 20 mg/month till 40 mg every other day dose achieved. Then taper 10 mg/month till 20 mg every other day achieved. Subsequent taper should be slow and maintain patient on 5 mg every other day or lower doses.
  - Tapering schedule should be individualised based on response and adverse effect. It should be slow in severe disease. Sense of wellbeing achieves immediately, but strength regains over 2–3 months.
- Steroid myopathy: When proximal lower limb weakness persists or increases after CK level has declined trend think of steroid myopathy. It will improve with modification of steroid doses. Patients should advice regular exercise program. Sometimes, there is overlap between active disease and steroid myopathy.

11.7.2 Other Immunosuppressants

Indications:

1. No improvement after 3–6 months of steroid therapy
2. Slow or incomplete improvement
3. Worsening on maintenance regime
4. Uncontrolled hypertension, diabetes, osteoporosis, obesity

Literature on immunosuppression in IIM:
Published randomized controlled trials are:

1. Placebo to azathioprine (Bunch et al. 1980), plasma exchange (Miller et al. 1992) or IVIg (Dalakas et al. 1993)
2. Methotrexate and azathioprine (Miller et al. 2002a, 2002b)
3. Cyclosporine and methotrexate (Vencovský et al. 2000)
4. Intravenous and oral methotrexate plus azathioprine (Bunch et al. 1980; Miller et al. 1992; Vencovský et al. 2000)
5. Etanercept (50 mg subcutaneously weekly) for 52 weeks (Muscle Study Group 2011)

Crossover study of IVIg in DM is available in positive-controlled trial (Villalba et al. 1998).

11.7.2.1 Methotrexate (MTX)

- Mechanism of action: Antifolate drug, inhibit lymphocyte proliferation
- Dose:
  - Starting dose is 7.5 mg per week orally. Maximum permissible dose is 25 mg per week. Depending on response, dose can be further increased 2.5 mg per week every week.
  - Intravenous or intramuscular dose should be considered in severe cases or non-responders. Dose is 0.4–0.8 mg/kg per week. Depending on response, dose can be increased by 5 mg per week. Maximum permissible dose is 60 mg per week.
  - Simultaneous administration of folic acid 0.8–1 mg per day orally or leucovorin parentally prevent side effects.
- Monitoring:
  - Improvement is noticed after 1–2 months of oral treatment.
  - Complete blood count, differential count and liver function test should be monitored every week for first month, then every month for next 6 months and then every 3 months.
- Adverse effects:
  - Stomatitis, bone marrow suppression, alopecia, pneumonitis, teratogenic effects, malignancy, infections, liver and renal dysfunction
- Caution:
  - Avoid in known ILD case or patients with positive Jo-1 antibodies.

11.7.2.2 Azathioprine (AZA)

- Mechanism of action: Inhibit T-lymphocyte proliferation
- Dose: 2–3 mg/kg/d (100–250 mg/day)
- Monitoring:
  - Improvement noticed after 4–8 months, maximum at 1–2 years.
  - Thiopurine methyltransferase: predict haematological toxicity, should not be given in homozygous; low dose can be given in heterozygous (Evans et al. 2001).
  - Complete blood count, differential count, MCV, liver function – at every week during first month, then every 15 days till 3 months, then every month till next 3 months and then every 3–6 monthly depending on treatment response (Booth et al. 2011)
- Side effects:
  - Flu-like hypersensitivity reaction, bone marrow suppression, liver dysfunction, pancreatitis, infection, malignancy, teratogenic effect

11.7.2.3 IVIg: Intravenous Immunoglobulin

- Mechanism of action: Immunomodulatory action on antibody, proinflammatory cytokines, Fc receptor, T cell, CD54 lymphocyte, macrophage colony-stimulating factor, monocyte chemotactant protein-1
- Dose: Initial dose – 2 g/kg divided over 2–5 days; maintenance dose – 0.4–2 g/kg per month depending on response (Dalakas et al. 1993)
- Indication: DM, PM, NM, refractory disease, steroid-sparing agent (Patwa et al. 2012)

Table 11.5 Newer molecules for treatment of IIM

Drug	Mechanism of action	Dose	Comments
Rituximab	Anti-CD 20 monoclonal antibody, exhaust B cell	2 doses 1 g in each dose 2 weeks apart	Double-blind (Oddis et al. 2013)
Etanercept infliximab	Anti-tumour necrosis factor agents	50 mg subcutaneous every week 310 mg/kg	Placebo-controlled trial of etanercept (Iannone et al. 2006; Muscle Study Group 2011) Retrospective uncontrolled studies for infliximab (Hengstman et al. 2003; Selva-O'Callaghan et al. 2004) Utility in IIMs limited (Hengstman et al. 2008; Riolo and Towheed 2012; Klein et al. 2010; Ishikawa et al. 2010)
Tocilizumab	Anti-IL6	8 mg/kg every 4 weeks	Case reports (Narazaki et al. 2011)
Alemtuzumab	Anti-CD 52 humanized monoclonal antibody	120 mg over 4 days One time course	Single case report (Kondo et al. 2014)
Abatacept	Inhibition of T cell co-stimulation	Varying dosage IV or subcutaneous	Clinical trial (ARTEMIS)
Sifalimumab	Anti-IFNα	0.3, 1, 3 and 10 mg/kg	One phase 1b controlled trial (Kerola and Kauppi 2015)

11.7.2.4 Cyclophosphamide

- Level of evidence: Open studies and case reports (Bombardieri et al. 1989; Cronin et al. 1989)
- Indication: Refractory cases, associated vasculitis cases

In addition to the medicines mentioned above, a variety of agents are in consideration and have been used in resistant cases (Table 11.5).

11.7.3 Interstitial Lung Disease

- First-line drug: Corticosteroids
- Second-line drugs: Mycophenolate mofetil, cyclosporine, tacrolimus
- Third-line drugs: Rituximab, cyclophosphamide

Mimori et al. (2012), Kotani et al. (2011), Marie et al. (2011)

11.7.4 Inclusion Body Myositis

- No guideline for management of IBM.
- Recommended therapy: Prednisone + methotrexate/azathioprine.
- There should be no contraindication to treatment.
- Treatment decision should consider general condition of patient.
- Avoid treatment in advanced case.

Mastaglia et al. (2003)

11.7.5 Rehabilitation

- Rehabilitation components: Physical and occupational therapy, orthotic devices, exercise (Varjú et al. 2003), creatine monohydrate supplementation (Chung et al. 2007)
- Resistive exercise: Active as well as chronic disease (Alexanderson et al. 2000; Alexanderson 2009)
- Passive range of motion exercises: Severe cases, prevent joint contracture
- Strengthening exercise: Mild to moderate cases, improving CK

11.8 Prognosis

- Outcome measures:
  - International Myositis Assessment and Clinical Studies Group (IMACS)
  - Pediatric Rheumatology International Trials Organization (PRINTO)

  Rider et al. (2011), Oddis et al. (2005), Isenberg et al. (2004).
- Poor prognostic factor for IIM: Older age, male, delay detection, dysphagia, cardiac involvement, associated malignancy, SANAM, ILD, Jo-1 antibody, SRP antibody, anti-155/140, anti CADM-140 antibody, anti Ro52 antibody (Yamasaki et al. 2011).
- Poor ILD prognostic factor: Older age, symptomatic ILD, lower values of vital capacity and diffusing capacity for carbon monoxide, a pattern of interstitial pneumonia on high resolution CT scan and lung biopsy and steroid-refractory ILD.
- Overall remission rate in PM/DM is 20–40% in treated patients (Bronner et al. 2006).
- Mortality rate two to three times higher than general population.
- Cause of mortality: Malignancy, pneumonitis, cardiac involvement, infections (Limaye et al. 2012).

In the authors' experience, acute and subacute presentations have better outcome than the insidious ones. Also, a large majority of sufferers remain on immunomodulation over prolonged periods of time, albeit on small doses.

11.9 Case Study

Clinical data: a 39-year-old male presented towards the end of 2014. He developed pain and weakness of the neck in mid-2013 which gradually increased. In mid-2014, he started experiencing considerable difficulty in holding his neck in upright position. His posture changed to accommodate the forward bending of neck. At this time, difficulties with shoulder also began and both shoulders (left > right) became weak. This affected his work in the later part of 2014. He also experienced breathlessness on walking. He was able to swallow and chew well, and symptoms did not fluctuate. He could turn in bed and had not experienced any weakness of lower parts of body. He did not have any sensory symptoms. During this year of 2014, he had lost 12–13 kilograms of body weight. His immediate family members did not report similar disease, and his parents were not consanguineous. He had been diagnosed to have Klinefelter syndrome during investigations for infertility.

His general examination was unremarkable, and there were no abnormalities of skin and joints. Neurological examination revealed profound weakness of the neck extensors and neck flexor muscles, and in the resting position, his neck remained flexed – neck drop. The trapezius, infraspinatus, supraspinatus, deltoids and serratus anterior muscles were weak, being weaker on the left side. He also had weakness of the forearm and finger extensors mainly on the right side (finger drop). The lower limb strength, in contrast, was almost normal with minimal weakness of the iliacus muscles on both sides. Deep tendon reflexes were well elicited, and the sensory system was normal. There were no fasciculations or tremors in upper limbs.

Summary: This 39-year-old male patient had a pure lower motor neuron weakness preferentially, affecting the neck and shoulder girdle muscles with prominent neck and finger drop.

Discussion: With this presentation, the possibilities of anterior horn cell disorder, neuromuscular junction disorders and inflammatory myopathy were explored.

Factors favouring

- Anterior horn cell disorder: Asymmetrical shoulder girdle weakness, neck drop and preserved reflexes
- Neuromuscular junction disorders: Prominent neck drop and weakness > wasting
- Inflammatory myopathy: Prominent neck drop, prominent finger drop, weakness > wasting, preserved reflexes and pain at the onset of illness

Factors not favouring

- Anterior horn cell disorder: Pain at the onset, weakness > wasting and absence of fasciculations and bulbar weakness
- Neuromuscular junction disorders: Absence of ptosis, bulbar weakness, fatigability and fluctuations
- Inflammatory myopathy: Asymmetrical shoulder girdle weakness, sparing of lower limbs and presence of finger drop

Diseases causing neck drop: Amyotrophic lateral sclerosis, myasthenia gravis, inflammatory myopathy, FSHD and nemaline myopathy

Diseases causing finger drop: Multifocal motor neuropathy with conduction block (MMN-CB), posterior interosseus neuropathy, FSHD, focal amyotrophy and slow channel myasthenia

Investigations revealed serum CK of 402 IU and positive ANA 1:160. Thyroid profile and acetyl choline receptor antibodies were normal. Electrophysiology showed myopathic potentials with increased insertional activity favouring inflammatory myopathy. MRI of the muscles of the upper limbs and neck showed abnormal signals of oedema suggestive of muscle inflammation. Left deltoid muscle biopsy showed evidence of inflammation with perimysial inflammatory cell exudates and myophagocytosis. Certain degree of fibrosis was also present. The Gomori trichrome stain did not show vacuoles or inclusions, and the immunostains against sarcoglycans, dysferlin and dystrophin were normal.

Final diagnosis: Atypical form of inflammatory myopathy – cervicobrachial polymyositis

Polymyositis usually involves pelvic girdle as well as shoulder girdle, while neck and bulbar group of muscles tend to be affected later on. But at times, inflammatory myopathies begin in shoulder and remain localized to upper girdle and neck. This group progresses slower than usual forms of polymyositis, and CK levels tend to be lower (mean CK 1275 IU). It responds well to immunosuppressive agents. This presentation can be mistaken for variety of other disorders, and appropriate treatment could be delayed.

Key Points

When to suspect

- Subacute or acute evolution of proximal muscle weakness often with dysphagia (IBM is chronic and asymmetrical, with brunt on quadriceps and wrist and finger flexors)
- Associated features of systemic diseases

How to investigate

- Elevated CK
- Electrophysiology showing spontaneous activity and myopathic potentials
- Muscle biopsy showing inflammatory cells engulfing the normal muscle fibres, vasculitis, perifascicular atrophy, inclusions
- Exclusion of a wide variety of diseases (Table 11.4)

How to treat

- Chronic immunotherapy

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Limb–Girdle Muscular Dystrophies

12

12.1 Introduction

Limb–girdle muscular dystrophies (LGMDs) are genetic muscle diseases characterised by slowly progressive weakness of hip girdle, thighs, shoulder girdle and proximal arms. Although proximal weakness is a prominent manifestation, it is not surprising to encounter marked distal muscle weakness in few subtypes of LGMDs. Although clinical phenotypes of some of the LGMDs may overlap, few subtypes of LGMDs have distinctive features such as cardiac dysfunction, distal muscle weakness, calf hypertrophy, joint contractures, asymmetrical weakness, etc. Based on inheritance patterns, there are two types: autosomal dominant (LGMD type 1) and autosomal recessive (LGMD type 2). Few LGMDs may show regional preponderance. At present, more than 25 different genes causing LGMD have been identified, and nomenclature of different LGMDs in an alphabetical manner has been done according to the chronology of identification of the genetic locus (Table 12.1). Since there is significant overlap in histopathological and immunohistochemical findings, genetic testing has evolved as the diagnostic test for LGMDs. Muscle imaging can help to detect the pattern of involved muscles and thus help to guide focused genetic testing. Till date, no specific treatment exists for LGMDs, and management of these diseases remains entirely supportive (Iyadurai and Kissel 2016; Nigro and Savarese 2014; Wicklund and Kissel 2014; Vissing 2016).

Uncommonly reported LGMDs are described below (Table 12.2).

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Table 12.1 Classification of LGMDs

Disease	Gene	Affected protein
Commonly reported autosomal dominant (AD) LGMDs (type 1)		
LGMD 1A (myotilinopathy)	MYOT	Myotilin
LGMD 1B (laminopathy)	LMNA	Lamin
LGMD 1C (caveolinopathy)	CAV3	Caveolin
Commonly reported autosomal recessive (AR) LGMDs (type 2)		
LGMD 2A (calpainopathy)	CAPN3	Calpain
LGMD 2B (dysferlinopathy)	DYSF	Dysferlin
LGMD 2C, 2D, 2E and 2F (sarcoglycanopathy)	SGCG, SGCA, SGCB and SGCD, respectively	Gamma-sarcoglycan, alpha-sarcoglycan, beta-sarcoglycan and delta-sarcoglycan
LGMD 2G (telethoninopathy)	TCAP	Telethonin
LGMD 2I (fukutin-related proteinopathy)	FKRP	Fukutin-related protein
LGMD 2 L (anoctaminopathy)	ANO5	Anoctamin 5
LGMD 2 M (fukutinopathy)	FKTN	Fukutin

Table 12.2 Uncommonly reported LGMDs

Disease	Gene	Protein	Inheritance
LGMD 1D (HSP40 proteinopathy)	DNAJB6	HSP40	AD
LGMD 1E (desminopathy)	DES	Desmin	AD
LGMD 1F (transportinopathy)	TNPO3	Transportin 3	AD
LGMD 1G (HNRPDL proteinopathy)	HNRPDL	Heterogeneous nuclear ribonucleoprotein D-like protein	AD
LGMD 1H	Gene locus 3p23	To be identified	AD
LGMD 2H (TRIM32 proteinopathy/sarcotubular myopathy	TRIM32	E3 ubiquitin ligase	AR
LGMD 2 J (titinopathy/Finnish distal myopathy)	TTN	Titin	AR
LGMD 2 K, 2 N, 2O and 2P (alpha-dystroglycanopathies)	POMT1, POMT2, POMGNT1 and DAG1	POMT1, POMT2, POMGNT1 and DAG1	AR
LGMD 2Q (plectinopathy)	PLEC1	Plectin	AR
LGMD 2R (desminopathy)	DES	Desmin	AR
LGMD 2S (TRAPPC11 proteinopathy)	TRAPPC11	Trafficking protein particle complex 11	AR
LGMD 2 T (GMPPB proteinopathy)	GMPPB	GDP-mannose pyrophosphorylase B	AR
LGMD 2 U (ISPD proteinopathy)	ISPD	Isoprenoid synthase domain containing	AR

POMT1 protein O-mannosyltransferase 1; *POMT2* protein O-mannosyltransferase 2; *POMGNT1* protein O-linked mannose 1,2-N-acetylglucosaminyltransferase; *DAG1* dystroglycan

12.2 Epidemiology

LGMDs have an incidence of 1–6 per 100,000 populations (Mah et al. 2016; Iyadurai and Kissel 2016). With the advent of genetic testing, whole genome sequencing in LGMDs has helped to evolve a pattern of regional distribution of LGMDs to some extent (Table 12.3).

Evolution of literature on LGMDs in India has been summarised below (Table 12.4).

Table 12.3 Geographical distribution of different types of LGMDs

Population subgroup	Common subtypes of LGMDs
India and other Asian countries	Sarcoglycanopathy, dysferlinopathy and calpainopathy are most commonly reported LGMDs from India and other Asian countries. Caveolinopathy and Fukutinopathy are prevalent in Japan
European countries	Anoctaminopathy, calpainopathy, Fukutin-related proteinopathy, dysferlinopathy and sarcoglycanopathy are common in European populations. LGMD 1F and LGMD 1H have been described from one Spanish and Italian family, respectively. Titinopathy has been described from Finland. Caveolinopathy has been reported from Spain, Sweden and the United Kingdom
United States	Calpainopathy, sarcoglycanopathy and dysferlinopathy are common types of LGMDs described from the United States
Brazil and South America	Dysferlinopathy, sarcoglycanopathy, telethoninopathy and LGMD 1G have been described from Brazil

Table 12.4 Salient Indian studies on LGMDs

Author (year)	Observations
Srinivas et al. (1975)	Out of 211 patients, 35 were found to have LGMD
Mondkar and Bhabha (1984)	Out of 126 patients with muscular dystrophy, 12 were designated as ‘girdle dystrophy’. Four cases (three males) with affected sisters were labelled as ‘autosomal recessive dystrophy of childhood’
Das (1998)	Out of 355 patients with dystrophy, 29.2% were labelled as LGMD
Dua (2001), Handa and Mital (2001), Joshi (2002)	With help of immunocytochemical studies, case reports of alpha-sarcoglycanopathy (adhalinopathy) were published
Gulati and Lekha (2003), Kapoor and Tatke (2005)	Case reports of beta- and gamma-sarcoglycanopathy have been reported
Khadilkar and Singh (2001), Khadilkar et al. (2002)	In these studies, sarcoglycanopathies were diagnosed based on immunohistochemistry. In these patients, hip adductors were significantly weaker than hip abductors, and a new observation of ‘hip abductor sign’ was made in sarcoglycanopathies
Sharma (2004), Meena (2007)	They reported 13 paediatric patients and 26 adults with sarcoglycanopathies, respectively

(continued)

Table 12.4 (continued)

Author (year)	Observations
Khadilkar et al. (2004)	In this study, 14 Indian patients were immuno-characterised as dysferlinopathy making it the first published study on dysferlinopathy
Pradhan (2008), Nalini (2008)	These studies published 9 and 28 patients, respectively, with dysferlinopathy
Khadilkar et al. (2008b)	A genetically confirmed case of dysferlinopathy first of its kind was published in 2008
Khadilkar et al. (2009)	First published data on spectrum of genetic mutations in sarcoglycanopathies
Pradhan (2006), Pradhan (2008)	In these studies, 'calf head on trophy' sign in Miyoshi myopathy and 'diamond on quadriceps' sign in dysferlinopathy were described
Pathak et al. 2010)	Immunohistochemically detected calpainopathy patients from North India were published
Ankala (2012), Khadilkar et al. (2016)	Founder mutation in calpainopathy in Agarwal population was described, and clinical utility of these genes was published in these studies, respectively
Nalini et al. (2015)	In a prospective study of immunophenotypic characterisation on LGMD, LGMD 2A–2 K were described

Pradhan and Khadilkar (2015), Khadilkar and Singh (2001), Khadilkar et al. (2002), Khadilkar et al. (2004, 2008a, 2008b, 2009, 2016), Pathak et al. (2010), Nalini et al. (2015)

12.3 Commonly Reported LGMDs

12.3.1 Clinical Features

Although proximal lower limb > upper limb–girdle weakness is most frequently occurring feature in all LGMDs, pattern of weakness and associated clinical features can help to differentiate amongst different subtypes of LGMDs. Clinical features of commonly reported LGMDs are tabulated below (Table 12.5).

As clinical features amongst different LGMDs overlap, some distinct phenotypic features occur in selected subtypes of LGMDs (Table 12.6).

It is not surprising that one genetic mutation can present with different phenotypes (Table 12.7).

12.3.2 Pathophysiology

Structural organisation of different proteins involved in LGMDs is depicted in Fig. 12.4. The protein and genes involved in pathogenesis of various LGMDs are summarised in Tables 12.1 and 12.2.

Table 12.5 Salient clinical features of commonly reported LGMDs

Disease	Age at onset	Pattern of weakness and wasting	Associated clinical features
LGMD 1A	Late onset varying from third to eighth decade	Distal + proximal; LL > UL; foot drop can be prominent; weakness of forearm, neck and facial muscles can occur	Joint contractures particularly at ankle; CM; dysarthria and respiratory involvement can be seen
LGMD 1B	Third to fourth decade; but can occur at younger age	Slowly progressive LL weakness; late involvement of UL	Cardiac abnormalities are very common; joint contractures, rigid spine and respiratory dysfunction can occur
LGMD 1C	Onset in first or second decade	Progressive symmetrical LL > UL muscle weakness; muscle hypertrophy is common	Muscle cramps on exertion and rippling of muscles on stretching or percussion are an important clinical clue
LGMD 2A	Usually in second or third decade	Proximal LL > UL; prominent scapular winging and sometimes, abdominal weakness can lead to hernia	Contractures occur commonly at ankle, but upper limb joints can be affected. Toe walking can occur in early stages (Fig. 12.1)
LGMD 2B	Late teens to early adulthood	Proximal LL > UL weakness; distal weakness (calf atrophy > foot drop) in later stages; milder involvement of upper limbs; inability to stand on toes	Can be of subacute onset; biceps lumps (Fig. 12.2); diamond on quadriceps; prominent myalgia and transient hypertrophy of calves and biceps before atrophy ensues
LGMD 2C–2F	Childhood onset	Proximal LL muscles (hip adductors and hamstrings) > UL muscles (biceps, deltoid and scapular muscles) and truncal muscle involvement	Prominent calves and proximal weakness form 'DMD'-like phenotype; scapular winging, distal weakness and CM can occur (Fig. 12.3)
LGMD 2G	Early onset in first or second decade	Proximal LL weakness; inability to stand in heels due to TA weakness and shoulder girdle weakness	Scapular winging; calf hypertrophy and cardiomyopathy are common
LGMD 2I	Onset from childhood to adulthood	Proximal LL > UL weakness; early diaphragmatic weakness	Calf and other muscle hypertrophy, respiratory failure and CM are common
LGMD 2 L	Adulthood (third to fifth decade onset)	Proximal LL > UL weakness; quadriceps and biceps are involved early	Asymmetrical weakness and atrophy is characteristic; frequently distal involvement in the form of calf atrophy is seen
LGMD 2 M	Early onset in first decade	Proximal muscle weakness; calf hypertrophy	Mental retardation, epilepsy, CM and eye abnormalities

LL lower limb; *UL* upper limb; *DMD* Duchenne muscular dystrophy; *CM* cardiomyopathy; *TA* tibialis anterior

Maggi et al. (2016), Khadilkar et al. (2016), Khadilkar et al. (2002), Bruno et al. (2012), Bushby (2009), Urtizberea et al. (2008), Iyadurai and Kissel (2016), Wicklund and Kissel (2014)

Table 12.6 Distinct phenotypic features in various LGMDs

Distinct phenotypic features	LGMD subtypes
Joint contractures	LGMD 1B, LGMD 1A, LGMD 2A
Rippling of muscles	LGMD 1C
Muscle cramps	LGMD 1C
Hip abduction splay	Described initially in LGMD 2C-2F but can occur in other LGMDs, e.g. LGMD 2B
Scapular winging	LGMD 2A, LGMD 2C-2F
Abdominal muscle weakness	LGMD 2A, LGMD 2C-2F, LGMD 2G
Cardiac involvement	LGMD 1B, LGMD 1A, LGMD 2C-2F, LGMD 2I, LGMD 1E and LGMD 2 M
Prominent lumps in muscle, e.g. biceps lump	LGMD 2B (diamond on quadriceps), LGMD 2A
Calf hypertrophy	LGMD 1C, LGMD 2C-2F, LGMD 2I, LGMD 2 M
Asymmetrical weakness and atrophy	LGMD 2 L (quadriceps, biceps and calves)
Prominent distal weakness	Calf atrophy – LGMD 2B, LGMD 2 L; Foot drop – LGMD 2 J, LGMD 1A, LGMD 1E
Mental retardation	LGMD 2 K, LGMD 2 M, LGMD 2 N, LGMD 2O and LGMD 2P
Respiratory involvement	LGMD 1A, LGMD 1B, LGMD 2C-2F, LGMD 2I and Pompe's disease

Shahrizaila et al. (2006), Iyadurai and Kissel (2016), Wicklund and Kissel (2014), Jackson CE (2008), Pradhan (2009)

Table 12.7 Different phenotypes caused by similar genetic mutations

Genotype	Affected protein	Different phenotypes
MYOT	Myotilin	LGMD 1A Myofibrillar myopathy (MFM)
LMNA	Lamin	LGMD 1B Emery–Dreifuss muscular dystrophy (EDMD) Congenital muscular dystrophy (CMD) Autosomal dominant dilated cardiomyopathy Rarely, lipodystrophy, mandibular dysplasia and progeria
CPN3	Calpain	LGMD 2A Asymptomatic hyperCKaemia
DYSF	Dysferlin	Miyoshi myopathy – refer Chap. 19 LGMD 2B – as described in Table 12.4 Proximodistal variant – prominent distal and proximal weakness at onset Distal myopathy with anterior tibial onset (DMAT) – onset in anterior leg muscle and later on, calf and proximal muscles can be affected
ANO5	Anoctamin	LGMD 2 L – refer Table 12.4 Distal myopathy – refer Chap. 19 Proximodistal weakness Proximal upper limb onset Asymptomatic hyperCKaemia

Table 12.7 (continued)

Genotype	Affected protein	Different phenotypes
FKTN	Fukutin	LGMD 2 M Fukuyama CMD
FKRP	Fukutin-related protein	LGMD 2I Walker–Warburg syndrome CMD with muscle hypertrophy
TTN	Titin	LGMD 2 J Autosomal dominant distal myopathy Autosomal dominant hereditary myopathy with early respiratory failure (HMERF)

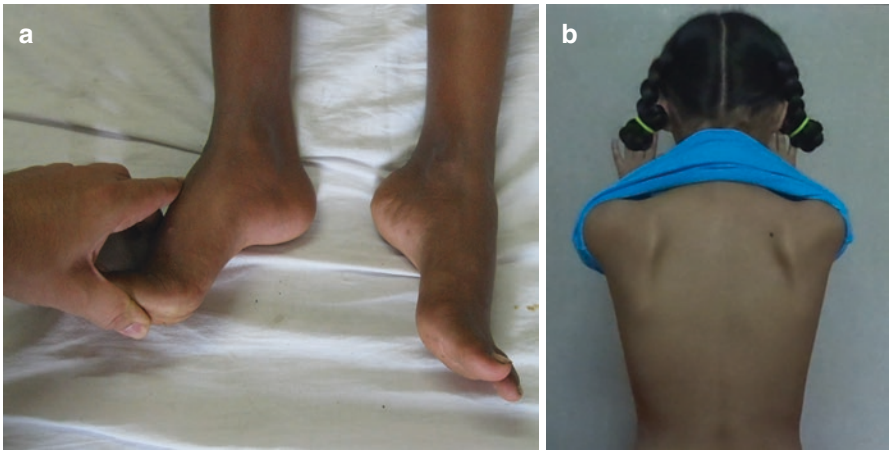

Fig. 12.1 (**a**) Ankle contractures and (**b**) scapular winging in a patient with LGMD 1A (calpainopathy)

12.3.3 Investigations

Routine workup of a patient presenting with limb–girdle weakness includes creatine kinase (CK) levels, nerve conduction study, needle electrode examination and muscle biopsy. Recent advances in imaging of skeletal muscles have helped to demonstrate differential involvement of muscles in few LGMDs. Cardiac workup and brain imaging may be required in certain cases. Detection of genetic mutations is diagnostic in most cases. An overview of investigational features is tabulated below (Table 12.8).

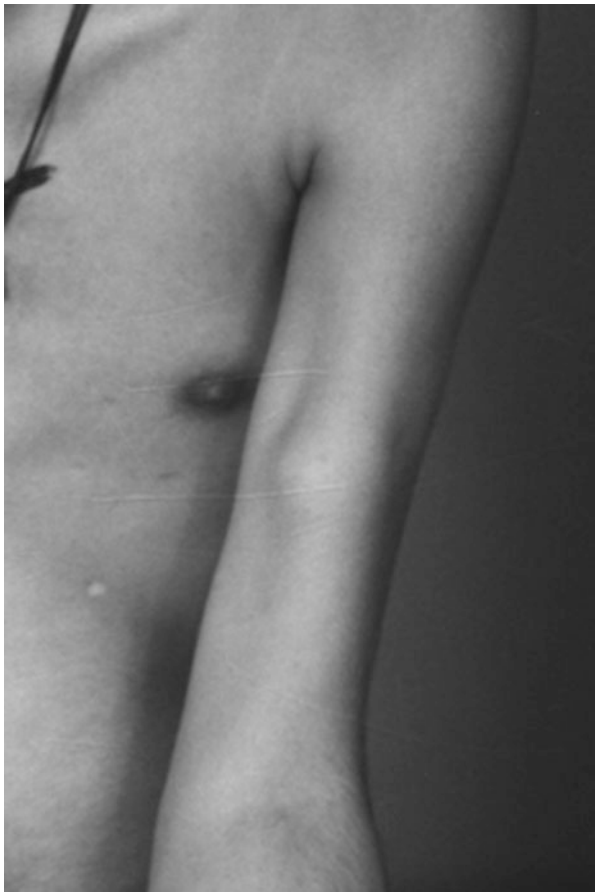

Fig. 12.2 Biceps lump in a patient with dysferlinopathy

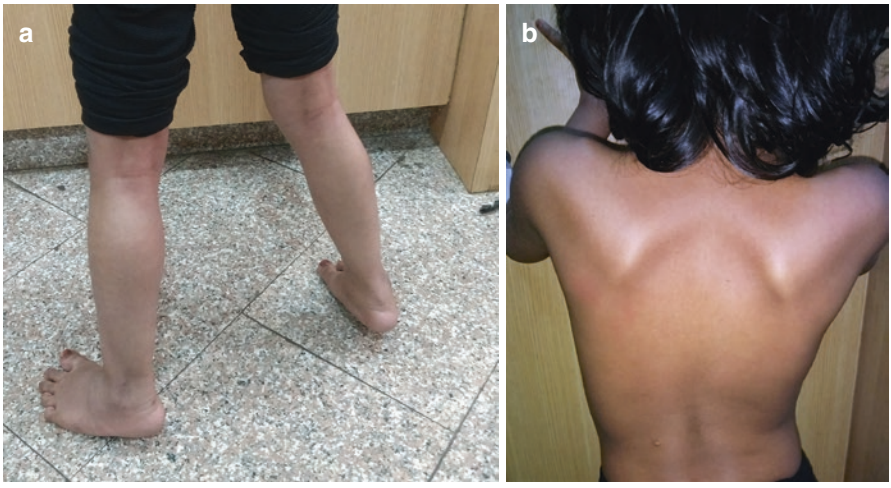

Fig. 12.3 (**a**) Calf hypertrophy, ankle contracture, tiptoe stance and (**b**) scapular winging in patient with LGMD 2F (delta-sarcoglycanopathy)

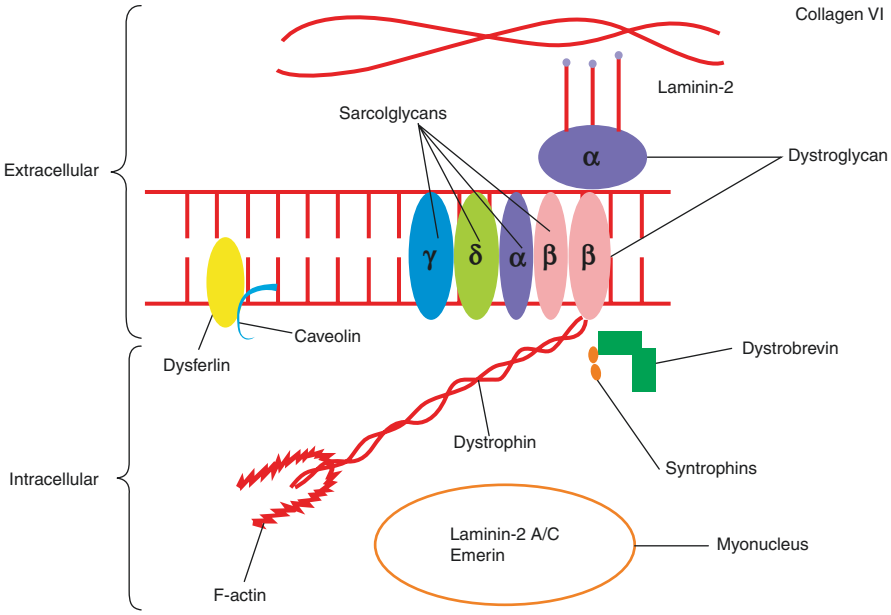

Fig. 12.4 Structural organisation of muscle proteins

Table 12.8 Salient investigational findings of commonly reported LGMDs

Disease	CK levels	Characteristic biopsy findings	Imaging pattern	Other tests
LGMD 1A	Mildly elevated	Dystrophic changes; rimmed vacuoles; desmin accumulation	Anterior and posterior leg; posterior thigh and gluteal muscles involved; semitendinosus and peroneal muscles are spared	ECG and 2D Echo can help to detect cardiac abnormalities
LGMD 1B	Normal to mild elevation	Dystrophic changes	Paraspinal, posterior thigh and leg muscles are severely affected; sparing of RF and anterior leg muscles	ECG shows conduction block and arrhythmia
LGMD 1C	Mildly elevated	Dystrophic changes; rarely inflammation	No specific pattern exists	Rippling of muscles is silent on NEE
LGMD 2A	Moderately to severely elevated	Dystrophic features; inflammation and presence of eosinophils can occur	Paraspinal, medial and posterior thigh, GM are affected early; vastus lateralis, sartorius and GL are spared	NEE shows increased insertional activity

(continued)

Table 12.8 (continued)

Disease	CK levels	Characteristic biopsy findings	Imaging pattern	Other tests
LGMD 2B	Severe to very severe elevations	Dystrophic features and inflammatory changes	GM, thigh adductors, vastus and glutei are affected early; GL, soleus, posterior thigh are affected at later stages	
LGMD 2C-2F	Moderately to severely elevated	Dystrophic features; rarely inflammation	Thigh adductors, hamstrings, glutei and psoas are effected early; vasti and leg muscles are spared	Cardiac workup in the form of ECG and 2D Echo
LGMD 2G	Moderate to severe elevations	Dystrophic features and rimmed vacuoles	Thigh adductors, anterior thigh, posterior thigh muscles, tibialis anterior and gastrocnemius affected	Cardiac workup in the form of ECG and 2D Echo
LGMD 2I	Severely elevated	Dystrophic features; type 1 fibre predominance	Glutei, vasti and posterior thigh and leg muscles are affected early	Cardiac workup and PFTs
LGMD 2 L	Severely elevated	Dystrophic features	Asymmetrical posterior thigh, hip adductors, GM and soleus affected early; GL and TA are also involved; RF, iliopsoas, sartorius are spared	
LGMD 2 M	Moderately to severely elevated	Dystrophic features	No specific pattern detected	MRI brain shows hypomyelination and migration defects; cardiac workup

ECG electrocardiogram; *NEE* needle electrode examination; *GM* gastrocnemius medialis; *GL* gastrocnemius lateralis; *PFTs* pulmonary function tests; *TA* tibialis anterior; *RF* rectus femoris
Cotta et al. (2014), Paim et al. (2013), Díaz-Manera et al. (2015), Iyadurai and Kissel (2016), Wicklund and Kissel (2014)

12.3.4 Differential Diagnosis

The clinical phenotype of proximal lower limb and upper limb weakness can be seen in LGMDs, other muscular dystrophies and various neuromuscular disorders. The presence of extraocular and facial weakness and other neurological and systemic features helps in differentiating LGMD from its mimics. Inflammatory

Table 12.9 Differential diagnosis of LGMDs and their key distinguishing features

Differential diagnosis	Key distinguishing features
Duchenne muscular dystrophy (DMD)	Occurs only in males; age at onset <6 years; knee extensors and hip abductors more commonly involved than knee flexors and hip adductors; early ankle and knee contracture; sparing of calves, brachioradialis, deltoid and infraspinatus; cardiac involvement in the form of tall R waves in V1–V3 favours DMD
EDMD	X-linked and autosomal inheritance; onset in the first to second decade; neck and elbow contractures; conduction abnormalities on ECG point towards EDMD
Adult-onset Pompe's disease	Presence of respiratory weakness out of proportion to limb–girdle weakness; exercise intolerance; absence of differential weakness; mildly elevated CK levels; characteristic histopathology features occur in adult-onset Pompe's disease
Facioscapulohumeral dystrophy (FSHD)	Autosomal dominant inheritance; presence of prominent facial, neck and scapular weakness at onset; milder involvement of LL as compared to UL; mildly elevated CK levels and presence of angulated fibres on muscle biopsy favour FSHD
Spinal muscular atrophy (SMA)	Please refer to case study in Chap. 10
Limb–girdle myasthenia	Presence of fatigability, fluctuations and ptosis; absence of differential weakness; normal CK levels; significant decrement on repetitive nerve stimulation (RNS) and normal muscle biopsy suggest limb–girdle myasthenia
CIDP with predominant motor involvement	Elderly onset; relatively shorter course of progressive weakness; areflexia; absence of differential weakness and muscle hypertrophy; normal CK levels; elevated cerebrospinal fluid (CSF) proteins; presence of demyelination on NCS and neurogenic potentials on NEE point towards CIDP

CIDP chronic inflammatory demyelinating neuropathies; *NCS* nerve conduction studies

myopathies (IM) are an important differential of LGMDs particularly dysferlinopathy as inflammatory cells are abundantly seen. Based on clinical features and laboratory findings, a scoring system has been designed to help differentiate between LGMDs and IIM. The advantage of the system is that it is based on clinical information and uses commonly available investigations (Khadilkar et al. 2008a) in this system; a score >14 suggests possibility of IM; score <8 favour muscular dystrophy; and score between 9 and 13 constitute the grey zone. Elevated CK values may not be helpful, as both diseases can present with CK values in thousands. The presence of inflammatory cells in normal muscle fibres on muscle biopsy occurs in IM. The presence of fibrillations and positive sharp waves favours presence of IM. Sustained response to corticosteroids occurs in IM, and thus, trial of corticosteroids can help to differentiate between LGMDs and IM in certain circumstances.

Other differential diagnoses of LGMDs with their key distinguishing features are described below (Table 12.9).

12.3.5 Management

Presently, no curative therapy exists for LGMDs. Corticosteroids and newer molecular therapies have not yielded promising results till now. Management of LGMDs requires a comprehensive approach towards cardiac function, respiratory function, nutrition, learning disabilities, spinal deformities and rehabilitation (Table 12.10). As these diseases are untreatable, molecular diagnosis, genetic counselling and prenatal diagnosis assume an important role in preventing transmission of these diseases from one generation to the other.

Table 12.10 Management of LGMDs

Cardiac function	It is important for clinicians that muscular dystrophies associated with cardiac involvement do not have symptoms such as chest pain, pedal oedema or palpitations but can contribute to significant morbidity and mortality. Some LGMDs tend to have higher association with cardiac abnormalities (Table 12.6). ECG, 2D Echo and Holter monitoring help in evaluation of rhythm and structural abnormalities of heart. Decision regarding pharmacological treatment, device placements and surgical intervention should be consulted with a cardiologist
Respiratory function	Respiratory functions should be monitored in all LGMDs patients with severe weakness, but few LGMDs tend to develop significant respiratory weakness (Table 12.6). Non-invasive ventilation should be considered for patients with excess daytime somnolence, frequent nocturnal arousals and morning headache due to respiratory insufficiency during sleep. Immunisation for common infections should be considered in order to prevent pulmonary infections. Chest infections should be treated promptly
Nutrition	Maintaining adequate nutrition and body weight is important as it can prolong survival in such patients
Learning disabilities	Few muscular dystrophies such as dystroglycanopathies often exhibit learning disabilities and cognitive dysfunction. Hence, neuropsychological testing and developmental paediatrics are needed to manage CNS involvement
Spinal deformities	Spinal deformities associated with LGMDs can lead to gait disturbances, respiratory dysfunction, disabilities and functional impairment. Hence, monitoring for progression of spinal deformities and surgical intervention may be considered in order to maintain normal posture, maintain cardiopulmonary function and optimize quality of life
Rehabilitation	Supervised aerobic exercise training can help to improve oxidative capacity and muscle function. Bracing and assistive devices can help to overcome dysfunction related to muscle weakness. Resistance training should be considered with caution as severe exertion can often lead to muscle damage. Rehabilitation can help to overcome joint contractures, scoliosis, osteoporosis, dysphagia, restrictive lung disease, obesity, metabolic syndrome and stress fractures
Genetic counselling	Molecular diagnosis of LGMD helps to detect asymptomatic carriers. Premarital genetic testing of relatives of diseases individuals and their partners can be useful to prevent transmission of disease from one generation to the other

Narayanaswami et al. (2014), Massalska et al. (2016), Siciliano et al. (2015), Straub and Bertoli (2016), Thompson and Straub (2016)

12.3.6 Prognosis

Few LGMDs are slowly progressive, and patients remain ambulatory till late into the illness, e.g. LGMD 1B, LGMD 2H and LGMD 2J. Cardiac and respiratory dysfunction can be prominent in few subtypes of LGMDs and can lead to morbidity and even mortality (Table 12.6). Overall, prognosis of LGMDs is dismal as there is no disease-modifying treatment available.

12.4 Uncommonly Reported LGMDs

Key clinical features and investigational findings of uncommonly reported LGMDs are described below (Table 12.11).

Table 12.11 Salient features of uncommonly reported LGMDs

Disease	Key clinical features	Key investigational findings
LGMD 1D	Adulthood-onset lower limb weakness; cardiac involvement is unusual and few patients can develop bulbar weakness	Mild to moderately elevated CK levels. Muscle biopsy may show rimmed vacuoles
LGMD 1E	Early to adulthood onset; slowly progressive proximal LL weakness; cardiac involvement is early and prominent	Mild to moderately elevated CK. Cardiac workup for CM and arrhythmias
LGMD 1F	Onset can occur from infancy to adulthood; shoulder girdle weakness and scapular winging can occur; distal weakness in late cases and respiratory impairment can occur early	Mild elevation in CK levels
LGMD 1G	Onset in adulthood; limitation of finger flexion is characteristic	Mild to moderate elevation in CK levels
LGMD 1H	Fifth decade onset; proximal LL and UL affected; calf hypertrophy and hyporeflexia can occur	CK levels can be normal but may show mild elevations
LGMD 2H	Described only in Hutterite population in North America; onset in the second or third decade; slow progression; remains ambulatory till the sixth decade, and contractures occur frequently	CK levels can be elevated up to 20 times of normal
LGMD 2 J	Onset in the second or third decade; onset in tibialis anterior; slow progression; absence of cardiomyopathy	Moderate to severely elevated CK levels; muscle MRI shows anterior leg involvement
LGMD 2 K, 2 N, 2O and 2P	Early onset in infancy and the first decade; proximal weakness; calf hypertrophy; cognitive abnormalities; epilepsy; contractures; microcephaly and eye abnormalities can occur	Moderate to severely elevated CK levels; MRI brain shows polymicrogyria, vermian hypoplasia and white matter abnormalities
LGMD 2Q	Childhood onset; proximal weakness; microcephaly and cognitive impairment	Mild to moderately elevated CK levels
LGMD 2R	Childhood onset; proximal weakness; prominent facial and respiratory involvement; scoliosis and cardiac abnormalities are very common	Mild to moderately elevated CK levels. Cardiac workup reveals conduction defects

(continued)

Table 12.11 (continued)

Disease	Key clinical features	Key investigational findings
LGMD 2S	Childhood onset; proximal weakness; scapular winging is often seen; chorea, ataxia and cognitive decline can occur	Mild to moderately elevated CK levels. MRI brain shows cerebral atrophy
LGMD 2 T	Variable age of onset of proximal weakness; hypotonia, intellectual disabilities and seizures in childhood and calf hypertrophy can occur	Elevated CK levels that can be aggravated by rhabdomyolysis
LGMD 2 U	Childhood onset; proximal weakness; relatively rapid progression; muscle hypertrophy and CM can occur	Mildly to moderately elevated CK levels; cardiac workup to detect CM

12.5 Case Study 1

Clinical details: A 21-year-old girl presented with gradually progressive proximal weakness in lower limbs more than upper limbs over a period of 10 years. No family members were affected. On examination, there was differential weakness affecting hip adductors more than hip abductors. Investigations revealed CK values of 392 U/L and myopathic potentials on NEE. Her ECG and 2D Echo were normal.

Summary: 21-year-old girl with limb–girdle weakness.

Discussion: Since this patient had no distinct phenotypic features (as mentioned in Table 12.6), that could suggest presence of particular subtype of LGMD. In such cases, it is unlikely for targeted genetic testing to yield a positive result. Hence, LGMD panel was tested, which showed pathogenic mutation in DNAJB6 gene. Final diagnosis of LGMD 1D was considered.

12.6 Case Study 2

Clinical details: A 42-year-old lady belonging to the Agarwal community had history of progressive proximal lower limb more than upper limb weakness, scapular winging and ankle contracture. For definitive diagnosis, genetic testing was offered and it showed homozygous mutation (c.2338 G>C, exon 22) in CAPN3 gene. She had a 23-year-old daughter, who was asymptomatic and was to get married. Their main concern was to know about chances of transmission of illness to the future generation.

Discussion: Patient was suffering from LGMD 2A caused by Agarwal founder mutation. Since she was suffering from autosomal recessive LGMD, chances of transmission to her daughter are 25% if her husband was a carrier. Genetic testing revealed that her daughter was an asymptomatic carrier for the same gene. Genetic testing of her partner did not show mutation in the same gene. Hence, the couple could be assured that their children would at the most be carriers and will not manifest disease. LGMD 2A forms a majority of LGMDs in the Agarwal community. Sensitivity of founder mutation in a patient of the Agarwal community presenting with LGMD phenotype is 89%. Testing the founder mutations can be used as the

first diagnostic test, bypassing the muscle biopsy in the Agarwals having LGMDs. It can be useful in carrier detection, counselling and offering community benefits at multiple levels.

Key Points

When to suspect

- Chronic progressive familial limb–girdle weakness
- Autosomal transmission
- Cardiomyopathies
- Distinct phenotypic features (Table 12.6)

How to investigate

- Variable elevation of CK
- Immunohistochemistry and Western blotting of muscle tissue
- Genetic panels

How to treat

- Prevention, prenatal advice and marriage counselling
- Supportive therapy

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Congenital Myasthenic Syndromes 13

13.1 Introduction

Congenital myasthenic syndromes (CMS) constitute a group of inherited disorders affecting the neuromuscular junction (Engel et al. 2015). Patients with CMS generally have onset at birth or early childhood; develop fatigable ocular, bulbar or limb–girdle weakness; and often have positive family history (Hantaï et al. 2004; Engel et al. 2015). The presence of repetitive compound muscle action potentials (CMAPs) on electrophysiology, lack of response to immunosuppressive agents, improvement with acetylcholinesterase (AChE) inhibitors in some patients or lack thereof and absence of anti-AchR and anti-MuSK antibodies point towards CMS (Abicht et al. 2016). Defect in neuromuscular transmission in CMS is caused by genetic mutations in molecules, located on the presynaptic, synaptic or postsynaptic segments of neuromuscular junction (Fig. 13.1). Around 20 genes causing CMS have been identified out of which, defects in acetylcholine receptor, endplate acetylcholinesterase deficiency and defects in endplate maintenance such as Dok-7 myasthenia and rapsyn deficiency are common forms of CMS. Many CMS subtypes have characteristic clinical and electrophysiological features. It is important to identify CMS subtype based on clinical, electrophysiological features and genetic mutations, as management and prognosis of each subtype differ from each other (Engel et al. 2015; Lorenzoni et al. 2012). Some CMS are frequently reported in various case series, e.g. primary Ach receptor deficiency, ChAT mutations, fast channel syndrome, etc., while CMS caused by GPFT1 and DPAGT1 mutations have been reported in few families. Based on location of molecular defects and frequency of occurrence, CMS can be classified into the following types (Table 13.1).

S.V. Khadilkar et al., *Neuromuscular Disorders*,
https://doi.org/10.1007/978-981-10-5361-0_13

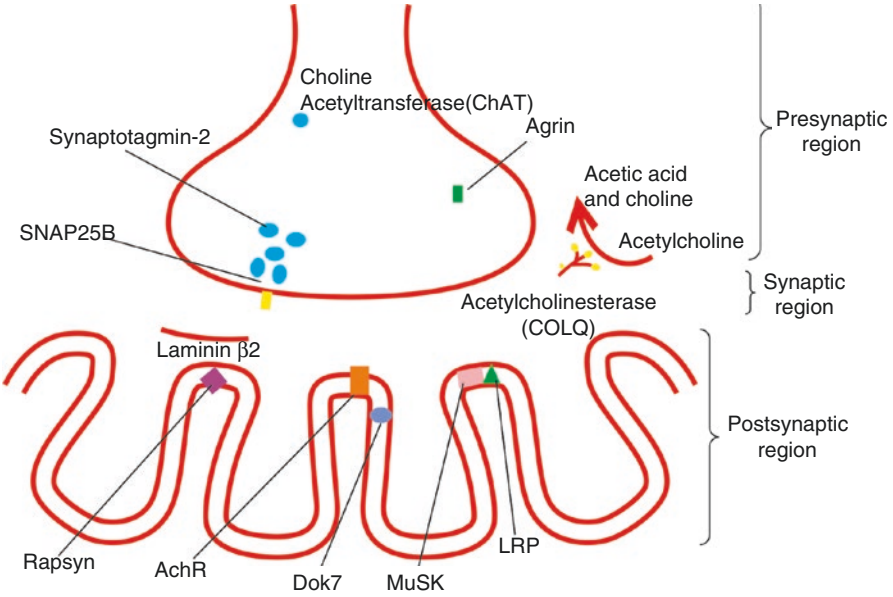

Fig. 13.1 Neuromuscular endplate with locations of pre-synaptic, synaptic and postsynaptic proteins involved in CMS

Table 13.1 Classification of CMS

Location of molecular defects	Common subtypes of CMS	Rare subtypes of CMS
Presynaptic	Choline acetyltransferase (ChAT) deficiency	Paucity of synaptic vesicles and reduced quantal release SNAP25B deficiency Synaptotagmin 2 deficiency
Synaptic basal lamina-associated	Endplate acetylcholinesterase deficiency (COLQ mutations)	Laminin-B2 (LAMB2) deficiency
Defects in acetylcholine (Ach) receptor	Primary Ach receptor deficiency (CHRNE, CHRNB and CHRNA1) Fast channel syndrome Slow channel syndrome	
Defects in endplate development and maintenance	Downstream of tyrosine kinase 7 (DoK-7) myasthenia Rapsyn deficiency	Agrin deficiency MuSK deficiency LRP4 myasthenia
Congenital defects of glycosylation		GPFT1 myasthenia; DPAGT1 myasthenia; ALG2 and ALG14
Other myasthenic syndromes		PREPL deletion; plectin deficiency; Na-channel myasthenia

13.2 Common Subtypes of CMS

As mentioned in Table 13.1, some genetic forms of CMS are frequently encountered and reported in literature. Details of relatively common forms of CMS are described in this section.

13.2.1 Epidemiology

Since the advent of molecular testing, genetically confirmed CMS cases have been reported from all parts of the world, particularly from the western countries. In a large cohort study of 680 CMS patients from a European centre, 81% of patients belonged to Europe. Small proportions of cases were from the United States, Asia and South America (Abicht et al. 2012). A large cohort of 321 patients of genetically confirmed CMS has been reported from a tertiary neuromuscular centre in the United States (Engel 2012). Commonly occurring forms of CMS encountered in this study were as mentioned in Table 13.1 (Engel et al. 2015; Engel 2012; Abicht et al. 2012). Estimated prevalence of genetically confirmed CMS in Europe is at least 3.8 per million populations (Finlayson et al. 2013). Small case series and case reports of CMS are available from Asia. From India, genetically confirmed cases of Dok7, rapsyn and CHRNE mutations have been published (Maramattom et al. 2014; Khadilkar et al. 2015; Singhal et al. 2008; Shankar et al. 2002). Based on clinical and electrophysiological profile, suspected cases of fast channel syndrome, slow channel syndrome and genetically unclassified CMS responsive to pyridostigmine and terbutaline have also been reported from India (Kumar and Kuruvilla 2010; Jagtap et al. 2013; Khwaja et al. 2000).

13.2.2 Clinical Features

CMS generally presents as fatigable ocular, bulbar, respiratory and limb–girdle muscle weakness which begins at birth or in early childhood. Clinical presentation varies with age at onset of illness and is described in Table 13.2.

The presence of positive family history helps to suspect CMS in a patient with fatigable weakness (Engel et al. 2015). However, in the large cohort described by Abicht et al., 80% of CMS patients had no documentation of affection of family members (Abicht et al. 2012). CMS is limited to weakness of skeletal muscles, while cardiac and smooth muscles are spared. Cognition, coordination, sensation and tendon reflexes remain unaffected. Some individuals can have dysmorphic facial features such as elongated face, narrow jaw and a high-arched palate (Abicht et al. 2016). Certain clinical features occur more commonly in some genetic forms of CMS. Presence of such features point to a particular candidate gene (Table 13.3).

Table 13.2 Clinical presentations of CMS

CMS presentations	Clinical features
Neonates	Lack of foetal movements in utero; respiratory insufficiency with sudden apnoea and cyanosis at birth; multiple joint contractures at birth described as 'arthrogryposis multiplex congenita'; ptosis, feeding difficulties, poor suck, poor cry, choking spells and stridor point towards ocular, facial and bulbar weakness. Patients can also have poor limb movements due to generalised weakness
Childhood	Fluctuating ptosis and extraocular muscle weakness; fatigable limb weakness with difficulty in running and climbing stairs; delayed motor milestones; bulbar weakness presenting as nasal speech with difficulty in swallowing and coughing; spinal deformity or muscle atrophy may occur
Limb–girdle myasthenia	Some patients develop a limb–girdle pattern of weakness and waddling gait with or without ptosis and ophthalmoparesis

Abicht et al. (2016)

Table 13.3 Clinical features of common subtypes of CMS

CMS subtypes	Clinical presentation	Diagnostic clues
Choline acetyltransferase (ChAT) deficiency	Neonatal hypotonia; episodes of bulbar weakness and apnoea at birth aggravated by infections, excitement or occurring spontaneously; many patients tend to improve with age and later on develop fluctuating ptosis and limb weakness	Episodic bulbar weakness and apnoeic spells
Endplate acetylcholinesterase deficiency (COLQ mutations)	Severe forms of illness present in early infancy; some patients with onset in childhood have milder illness; few patients have limb–girdle presentation	Delayed pupillary light response is noted in a proportion of patients
Primary AchR deficiency (CHRNE mutation)	Early onset; most patients have ptosis, ophthalmoparesis and moderate to severe limb weakness	Ptosis and extraocular muscle weakness is present in higher proportion of patients
AchR kinetic abnormalities (CHRNE, CHRNA1, CHRNB1 and CHRND mutation)	Fast channel syndrome: onset at birth; mild to severe illness and autosomal recessive inheritance Slow channel syndrome: onset in the first decade to adulthood; severe involvement of forearm, scapular and cervical muscles; relative sparing of ocular muscles; autosomal dominant inheritance	Wrist and finger extensor and neck weakness point to slow channel syndrome. No particular clue for fast channel syndrome
Dok-7 mutation	Mild to severe illness; onset in childhood to adulthood; predominant limb–girdle weakness with relative sparing of ocular and bulbar muscles. Some patients may develop wasting in later stages	Limb–girdle myasthenia with mild ptosis

Table 13.3 (continued)

CMS subtypes	Clinical presentation	Diagnostic clues
Rapsyn mutation	Most patients have onset in infancy and present with neonatal hypotonia, episodic apnoea, and multiple contractures Late-onset cases have predominant limb–girdle weakness	Episodic apnoea in infancy and limb–girdle weakness in adulthood with sparing of ocular muscles

Engel (2012), Engel et al. (2015), Abicht et al. (2012), Hantaï et al. (2004, 2013), Abicht et al. (2016)

13.2.3 Pathophysiology

In normal individuals, one molecule of Ach is released from the presynaptic nerve terminal into the synaptic cleft, and it binds to Ach receptor on the postsynaptic membrane on the muscle fibre. Binding of Ach to Ach receptor leads to transient opening of voltage-gated ion channels associated with Ach receptor. After the channel returns to closed state, Ach diffuses into synaptic cleft, is hydrolysed by AChE and cleared from synaptic cleft. The depolarisation of skeletal muscle fibres caused by binding of Ach to Ach receptor, i.e. endplate potential (EPP), is more than the depolarisation required to activate voltage-gated ion channels on the postsynaptic membrane. The difference between these values is known as 'safety margin' of neuromuscular transmission. Safety margin is determined by quantal release of Ach, functional state of AChE in synaptic cleft, concentration and kinetic properties of Ach receptor and voltage gated sodium channels. Mutations in genes encoding proteins involved in any one or more of these mechanisms reduce the safety margin and cause neuromuscular transmission defect. Genetic mutations affecting proteins located on presynaptic, synaptic or postsynaptic terminals in CMS are mentioned in Table 13.4.

Engel et al. have described the role of each of these molecules in pathogenesis of CMS in their review paper Engel et al. (2015)

13.2.4 Investigations

Investigations can further help in assessing the CMS subtype. Patients with CMS are tested negative for anti-AchR and anti-MuSK antibodies. Decremental response of CMAPs occurs in a large proportion of CMS patients on 2–3 Hz repetitive nerve stimulation (RNS) (Abicht et al. 2012, 2016) presence of extra discharge following CMAP should arouse suspicion of CMS (Fig. 13.2). Decrement more than 50% is seen after a subtetanic stimulation at 10 Hz for 5 min and followed by slow recovery over 5–10 min points to ChAT deficiency (Engel et al. 2015). Single fibre electromyography (SFEMG) helps in confirming neuromuscular transmission defect in a patient with suspicion of CMS. However, the abnormalities detected on SFEMG need to be interpreted with caution. Elicitation of repetitive CMAPs on a single nerve stimulus is encountered in patients with slow channel syndrome and COLQ

Table 13.4 Genetic mutations and affected proteins in CMS

Location of molecular defects	Protein	Gene
Presynaptic	Choline acetyltransferase deficiency	CHAT
Synaptic	Endplate cholinesterase deficiency	COLQ
Postsynaptic	Primary Ach receptor deficiency; slow channel syndrome; fast channel syndrome	CHRNA1; CHRNB1; CHRND; CHRNE
	Dok-7 myasthenia	DOK7
	Rapsyn deficiency	RAPSN

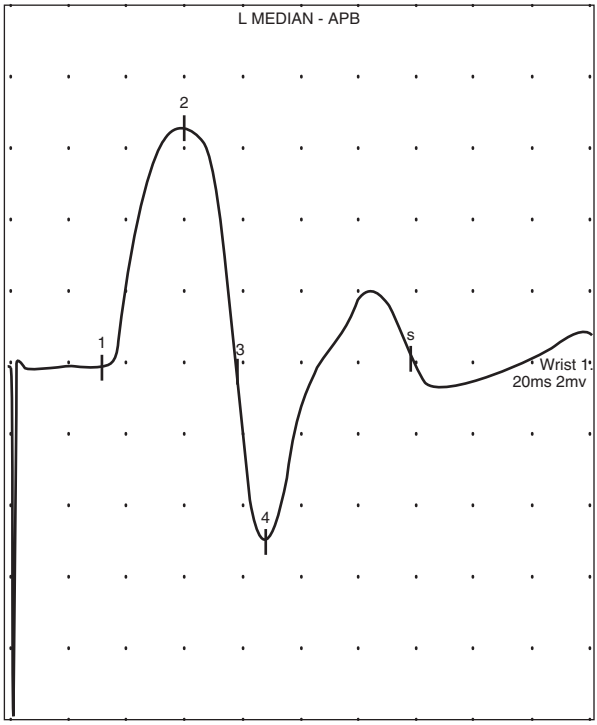

Fig. 13.2 Extra discharge (*arrow*) noted following the CMAP in a patient with congenital myasthenic syndrome (Courtesy: Dr. Khushnuma Mansukhani, Bombay Hospital, Bombay)

gene mutation (Fig. 13.1). Creatine kinase (CK) levels are normal or slightly elevated in patients with CMS (Abicht et al. 2016; Engel et al. 2015). When clinical or electrophysiological studies point to a particular subtype of CMS, appropriate genetic tests help in the confirmation of diagnosis.

13.2.5 Differential Diagnosis

Due to treatable nature of illness, it is important to consider CMS in the differential diagnosis of neonatal- and childhood-onset neuromuscular weakness. Differential diagnoses of floppy infant with their key differentiating features are mentioned in

Table 13.5 Differential diagnosis of CMS with their key distinguishing features

Diseases	Key differentiating features
Myasthenia gravis (MG)	Female preponderance in the second or third decade onset, fluctuating asymmetrical ptosis and ophthalmoparesis, absence of repetitive CMAPs and presence of AchR antibodies favour autoimmune MG. Presence of positive family history favours CMS
Lambert–Eaton myasthenic syndrome (LEMS)	Mild and less common ocular and bulbar involvement, prominent limb weakness at onset, pain in limbs, autonomic dysfunction, sensory complaints, transient improvement with exercise, depressed reflexes, more than 100% increment on RNS and presence of tumours such as small cell lung carcinoma favour LEMS
Mitochondrial disorders	Slowly progressive, symmetrical, nonfluctuating and nonfatigable ptosis, early slowing of saccades and ophthalmoparesis. Associated features are retinal degeneration; ataxia and cardiac involvement are seen in CPEO
Muscular dystrophy forms a close differential of limb–girdle myasthenia	Slowly progressive, nonfatigable and nonfluctuating lower limb > upper limb weakness, sparing of ocular group of muscles, absence of repetitive CMAPs or decrement on RNS and elevated CK levels favour muscular dystrophy

the chapter of spinal muscular atrophy. A small proportion of patients with CMS patients have onset in adolescence or adulthood and should be differentiated from other diseases as mentioned in Table 13.5.

13.2.6 Management

Treatment strategies for CMS include medical therapy and comprehensive rehabilitation program. It is important to select appropriate medications as therapy useful in one subtype of CMS can worsen other subtypes.

13.2.6.1 Medications

Medications that are useful to treat CMS are mentioned in Table 13.6. From a practical standpoint, initiation of acetylcholine esterase inhibitors should be done in very small titrated doses and increased in a graded manner, as there is a distinct possibility of deterioration. Occasionally, a patient may show much deterioration, and it is useful to line out in patient help beforehand. Beta agonist also should be started in smaller doses and increased slowly. It is important to appreciate that the benefit of these agents can be very gradual. For example, some patients with DOK-7 disease show gradually improving performance over 2–3 months, eventually reaching the maximum. Hence, briefer trials could be erroneous. Quinidine and related medicines require cardiac monitoring.

13.2.6.2 Supportive Management

Multidisciplinary approach for rehabilitation can be useful to reduce disability and improve quality of life. Physical, occupational therapy and orthotics help to

Table 13.6 Medications in CMS

Medications	Mechanisms	Use in CMS
Acetylycholinesterase (AChE) inhibitors	Inhibits AChE in synaptic cleft and increase in Ach concentration	Useful in AchR deficiency, ChAT deficiency and fast channel syndromes. AChE inhibitors can worsen following subtypes of CMS: slow channel syndrome, Dok-7 myasthenia and COLQ mutations
Beta agonists like salbutamol, terbutaline and ephedrine	Through activation of MuSK, it helps in neuromuscular synaptogenesis and maintenance	Patients with COLQ mutation and Dok-7 myasthenia show improvement with salbutamol. In a proportion of patients with AchR deficiency, salbutamol can be helpful
Amifampridine	Increases release of Ach quanta released by each nerve impulse	Beneficial in AchR deficiency and fast channel syndromes
Quinidine and fluoxetine	Block long-lived open channels and, hence, duration of prolonged synaptic currents. Thus, they prevent depolarisation block and desensitise AchR and enhance transmission	Useful in CMS subtypes such as slow channel syndrome that is worsened with other medications. Fluoxetine is a drug of choice, but quinidine can be considered when psychiatric side effects of fluoxetine form a limitation

Engel et al. (2015) and Abicht et al. (2016)

overcome disability associated with fixed deficits. Speech and swallowing difficulty due to bulbar weakness can be mitigated with speech therapy and nasogastric tube. Patients with episodes of respiratory weakness may require use of ventilatory support judiciously. As in MG, agents that can worsen neuromuscular weakness should be avoided. Patients may also require monitoring for possible cardiac side-effects of therapeutic agents. Family members of patients should be evaluated, as these disorders show autosomal pattern of inheritance (Abicht et al. (2016)).

13.2.7 Prognosis

Course of CMS can vary from mild illness to severe disabilities and respiratory failure. Patients have fluctuating course of illness as respiratory failure can be precipitated by fever, infections or medications in some subtypes of CMS. Patients with limb–girdle myasthenia may progress to develop severe disabling requiring rehabilitation. Response to therapy is favourable, and selection of appropriate therapeutic agents is important.

13.3 Rare Forms of CMS

Some subtypes of CMS have been described in few families and from a small proportion of this heterogeneous group of illnesses. These subtypes of CMS with their key features are described in brief (Table 13.7).

Table 13.7 Key features of rare subtypes of CMS

Subtypes of CMS	Key features
SNAP25B deficiency	First reported in African-American patients; onset at birth; multiple contractures; delayed milestones; improvement with amifampridine
Synaptotagmin 2 deficiency	Childhood-onset foot deformities, fatigable weakness, depressed tendon reflexes; low compound muscle action potentials with postexercise facilitation
Laminin-B2 (LAMB2) deficiency	Only one report describing this subtype is available. Patient had associated ocular and renal involvement
Agrin deficiency	It is caused by AGRN gene mutation. It has been reported in seven families. Early childhood ptosis, facial and limb–girdle weakness; wasting of muscles can occur in advanced cases; pyridostigmine should be used with caution; partial improvement can occur with ephedrine
LRP4 myasthenia	Single case reported; patient had respiratory weakness at birth and fatigable weakness of limb–girdle muscles; pyridostigmine and amifampridine should be avoided
Disorders of glycosylation	GPFT1 myasthenia: Patients usually develop slowly progressive limb–girdle weakness; responds to pyridostigmine DPAGT1 myasthenia: Patients can have intellectual disability; may respond to pyridostigmine and salbutamol ALG2 and ALG14: Reported in one family These patients have tubular aggregates of sarcoplasmic reticulum in muscle fibres
PREPL deletion	Reported patients had ptosis, poor feeding, bulbar weakness, cystinuria, growth hormone deficiency and responded to pyridostigmine
Plectin deficiency	Reported patients had progressive weakness and epidermolysis bullosa simplex; responded poorly to pyridostigmine
Na-channel myasthenia	One patient had brief, abrupt onset of muscle weakness and respiratory arrest at birth; pyridostigmine and acetazolamide can be helpful
Myasthenia associated with congenital myopathies	Ocular muscle weakness, facial weakness, exercise intolerance, decremental response on RNS and improvement with pyridostigmine were noted in some patients with centronuclear myopathy caused by myotubularin and dynamin 2 mutations

Engel et al. (2015) and Abicht et al. (2016)

13.4 Case Study

Clinical details: A 10-year-old girl presented with history of delayed motor milestones and learned to walk at 2 years of age. Parents noticed her gait to be different. Over the next 8 years, she developed steadily progressive, proximal and distal weakness of both lower limbs, leading to difficulty in getting up from sitting position. Due to neck and truncal weakness, she needed support while getting up from supine position. Mother also mentioned that she lacked stamina and was easily exhausted. At the time of presentation, she was not able to lift her arms above shoulder level and could barely walk 50 m with severe lordosis and waddle. There were no fluctuations and course was steadily progressive. She did not have ptosis, ophthalmoparesis, facial or pharyngeal weakness, fasciculations, tremulousness of hands or sensory involvement. On examination, external ocular movements and facial and pharyngeal muscles were normal. Neck flexors and extensors were MRC grade 3/5. Power in proximal upper limb muscles was 3/5, proximal lower limb muscles were 2/5 and distal muscles were 4/5. All deep tendon reflexes were depressed. Her 8-year-old brother had similar issues but was less severely affected. She was born of nonconsanguineous marriage.

Summary: Familial, early onset, gradually progressive limb–girdle weakness without any cranial nerve involvement.

Discussion: Since the patient had lower motor neuron type of weakness, possibilities of anterior horn cell disorder (SMA II), primary muscle diseases and neuromuscular junction disorder were considered. Her CK value was 93 U/L, NEE showed myopathic potentials and muscle biopsy did not yield any specific changes. Additional clue on history that 'apart from weakness, both the children got easily tired while walking and carrying out daily activities and with rest, these complaints subsided', helped in prioritising localisation. Patient underwent RNS. Low-frequency RNS demonstrated significant (25%) reduction in motor amplitudes. Anti-AchR and anti-MuSK antibodies were negative. With suspicion of 'limb–girdle myasthenia', genetic testing for Dok-7 was ordered, which showed mutation in Dok-7 gene (C.601C > CT) on chromosome 4 in both siblings. Patient was started on salbutamol (0.1–0.3 mg/kg day) 2 mg ½ tablets thrice a day and gradually increased to one tablet thrice a day. Patients showed remarkable improvement in their muscle power and functional status even though treatment was started late in the course of illness. No adverse effects were noted. Pyridostigmine was avoided, as it is known to worsen Dok-7 myasthenia. Thus, phenotypic clues helped in targeted genetic testing and selection of therapy (Table 13.3) in this family.

Key Points

When to suspect:

- Early life neuromuscular syndrome
- Familial
- Fatigability
- Extramuscular clues (Table 13.3)

How to diagnose:

- Decrementing response
- Repetitive CMAPs
- Absence of AchR and MuSK antibodies
- Mutation analysis

How to treat:

- Depending upon the clinical and electrophysiological features (Table 13.6)
  - Pyridostigmine
  - Salbutamol
  - Fluoxetine
  - Amifampridine

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Congenital Muscular Dystrophies 14

14.1 Introduction

CMDs are a group of clinically and genetically heterogeneous disorders characterised by congenital hypotonia, delayed motor developmental milestones and early onset of progressive muscle weakness, associated with dystrophic pattern on muscle biopsy (Reed 2009). CMD was first described by Batten (Batten 1903), while Howard (Howard 1908) coined the term 'dystrophia muscularis congenita'. In mid-1990s various CMDs with brain and eye involvement emerged (Walker 1942; Fukuyama et al. 1960; Santavuori et al. 1977; Warburg 1976). Amongst these, an 'occidental type cerebromuscular dystrophy' with near normal intelligence was also described (Topaloglu et al. 1990). Since 1999 various genetic defects responsible for different phenotypes of CMDs have been elucidated. Current classification of CMDs is based on biochemical and genetic defects (Table 14.1). However, as a single gene can be associated to a number of different phenotypes, for the clinician it is more useful to describe the subtypes according to the combination of clinical aspects and primary or secondary protein defects.

14.2 Epidemiology

Although frequency of various CMDs shows regional and ethnic variations, MDC1A and Ullrich myopathy are amongst the most common phenotypes in European countries and Brazil (Pepe et al. 2002; Muntoni and Voit 2004; Ferreira et al. 2005). Fukuyama CMD is the most common CMD in japan. The rare subtypes of CMD are MDC1D, CMD which result from primary alpha-7 integrin deficiency, and MDC1B, respectively.

S.V. Khadilkar et al., *Neuromuscular Disorders*,
https://doi.org/10.1007/978-981-10-5361-0_14

Table 14.1 Classification of CMDs

Disorder	Protein	Gene	Chromosome
Defects of glycosylation (alpha-dystroglycanopathies)			
Muscle–eye–brain disease	O-linked mannose β1.2-N-acetylglucosaminytransferase	POMGnT1	1p32-p34
Walker–Warburg syndrome	Protein-O-mannosyltranferase1	POMT1	9q34
	Protein-O-mannosyltranferase2	POMT2	14q24
	Fukutin	FCMD	9q31-q33
	Fukutin-related protein	FKRP	19q13.3
	LARGE	LARGE	22q12.3-q13.1
Fukuyama CMD (FCMD)	Fukutin	FCMD	9q31-q33
CMD with muscle hypertrophy (MDC1C)	Fukutin-related protein	FKRP	19q13.3
CMD with severe intellectual impairment and abnormal glycosylation	LARGE	LARGE	22q12.3-q13.1
Defects of structural proteins			
UCMD1/Bethlem myopathy	Collage VI	Col 6A1	21q22.3
UCMD2/ Bethlem myopathy	Collage VI	Col 6A2	21q22.3
UCMD3/ Bethlem myopathy	Collage VI	Col 6A3	2q37
Merosin-deficient CMD (MDC1A)	Lamininα2	LAMA2	6q22-q23
Integrin α7-deficint CMD	Integrin α7	ITGA7	12q13
CMD with joint hyperlaxity	Integrin α9	ITGA9	3p23-21
CMD with epidermolysis bullosa	Plectin	Plectin	8q24.3
Proteins of the ER and nucleus			
Rigid spine syndrome	Selenoprotein N1	SEPN1	1p35-p36
LMNA-deficient CMD	Lamin A/C	LMNA	1q21.2
Other			
CMD with respiratory failure and muscle hypertrophy			1q42

UCMD Ullrich CMD, *ER* endoplasmic reticulum

14.3 Clinical Features

Due to the clinical heterogeneity of CMDs, the first step towards obtaining the correct diagnosis of a particular subtype is analysis of the key clinical features: CNS involvement, eyes involvement, degree of clinical severity and progression, spine deformities and respiratory issues, distribution of joint contractures and/or joint laxity, presence of muscle hypertrophy and skin changes. These neuromuscular and non-neuromuscular features are enumerated in Tables 14.2 and 14.3.

Table 14.2 Neuromuscular clinical features of CMDs

Disorder	Inheritance	Age of onset	Weakness pattern	Contracture	Joint hyperlaxity
Defects of glycosylation					
Muscle–eye–brain disease	AR	Neonatal	Generalised	Elbows	No
Walker–Warburg syndrome	AR	Neonatal	Generalised; severe	Elbows	No
Fukuyama CMD (FCMD)	AR	Neonatal	Generalised	Hips, knee, ankles and elbow	No
CMD with muscle hypertrophy (MDC1C)	AR	Birth to 6 months	Generalised arms > legs	Elbow, knee, fingers	No
CMD with severe intellectual impairment and abnormal glycosylation (MDC1D)	AR	Within the first year of life	Generalised	Mild at ankle and elbow	No
Defects of structural proteins					
UCMD	AR	Birth to infancy	Generalised; distal > proximal	Hips, knee, fingers, elbows	Yes
Bethlem myopathy	AD	Neonatal, childhood to adolescent	Generalised proximal > distal	Interphalangeal joint, elbow, ankle (Fig. 14.1)	
Merosin-deficient CMD (MDC1A)	AR	Birth; partial deficiency can present at 1–12 years of age	Generalised	Multiple; not severe	No

(continued)

Table 14.2 (continued)

Disorder	Inheritance	Age of onset	Weakness pattern	Contracture	Joint hyperlaxity
Integrin α7-deficient CMD	AR	Birth to 2 months	Proximal	Torticollis	No
CMD with joint hyperlaxity	AR	Birth	Generalised; progressive	Ankles, knees, shoulders	Yes
CMD with epidermolysis bullosa	AR	Birth to 20 years	Generalised, facial muscles	No	No
Proteins of the ER and nucleus					
Rigid spine syndrome	AR/AD	Infancy	Axial, neck and facial muscles	Elbow and ankle	No
LMNA-deficient CMD	Possible AD	Infancy	Axial muscles dropped head, proximal in upper limbs, distal in lower limbs	Distal–proximal lower limb sparing elbow	No
Others					
CMD with respiratory failure and muscle hypertrophy	Possible AR	Birth to infancy	Proximal with marked cervical involvement	Achilles tendon contracture	No

Table 14.3 Non-neuromuscular clinical features of CMDs

Disorder	Eye findings	Seizure/mental retardation	Others
Defects of glycosylation			
Muscle–eye–brain disease	Myopia, retinal dysplasia	Both	Dysmorphic features
Walker–Warburg syndrome	Microphthalmia, coloboma, cataracts	Both	In males gonadal and genital defects, rarely dysmorphic features and cleft palate
Fukuyama CMD (FCMD)	50% mild to severe	Both	Dilated cardiomyopathy, hypertrophy of calves, quadriceps, tongue
CMD with muscle hypertrophy (MDC1C)	No	None	Calf, quadriceps, tongue hypertrophy, muscle cramps, cardiac involvement
CMD with severe intellectual impairment and abnormal glycosylation (MDC1D)	Abnormal ERG	MR	Calf, thigh, shoulder girdle, tongue muscle hypertrophy

Table 14.3 (continued)

Disorder	Eye findings	Seizure/mental retardation	Others
Defects of structural proteins			
UCMD	No	None	Dysmorphic features, prominent heels, velvety palms, scoliosis, early respiratory involvement, sandpaper skin, torticollis, congenital hip dislocation
Bethlem myopathy	No	None	Hyperkeratosis, keloid formation (Fig. 14.1)
Merosin-deficient CMD (MDC1A)	Occasionally VER abnormal	Both	Dysmorphic features, rare cardiac involvement
Integrin α7-deficint CMD	No	MR	–
CMD with joint hyperlaxity	No	None	–
CMD with epidermolysis bullosa	No	None	Haemorrhagic blisters and erosions over the skin
Proteins of the ER and nucleus			
Rigid spine syndrome	No	None	Limited spine flexion, progressive scoliosis, respiratory failure
LMNA-deficient CMD	No	None	Cardiac arrhythmias, respiratory failure, rigid spine, talipes foot deformity
Others			
CMD with respiratory failure and muscle hypertrophy	No	None	Muscle hypertrophy

14.4 Pathophysiology

Dystrophin glycoprotein complex is a large assembly of proteins which spans through the sarcolemma of muscle fibres and acts as link between extracellular matrix and contractile protein actin (Cohn 2005; Ervasti and Sonnemann 2008). This complex contains dystroglycan which has two components: beta and alpha-DG. Dystroglycan attaches sarcolemma to the basement membrane, and to do that it has to undergo glycosylation. This process involves various glycosyltransferases enzymes. Mutation in genes coding for these enzymes is responsible for five CMDs named as alpha-dystroglycanopathies (Table 14.1). After glycosylation, alpha-dystroglycan attaches to basement membrane via laminin 2

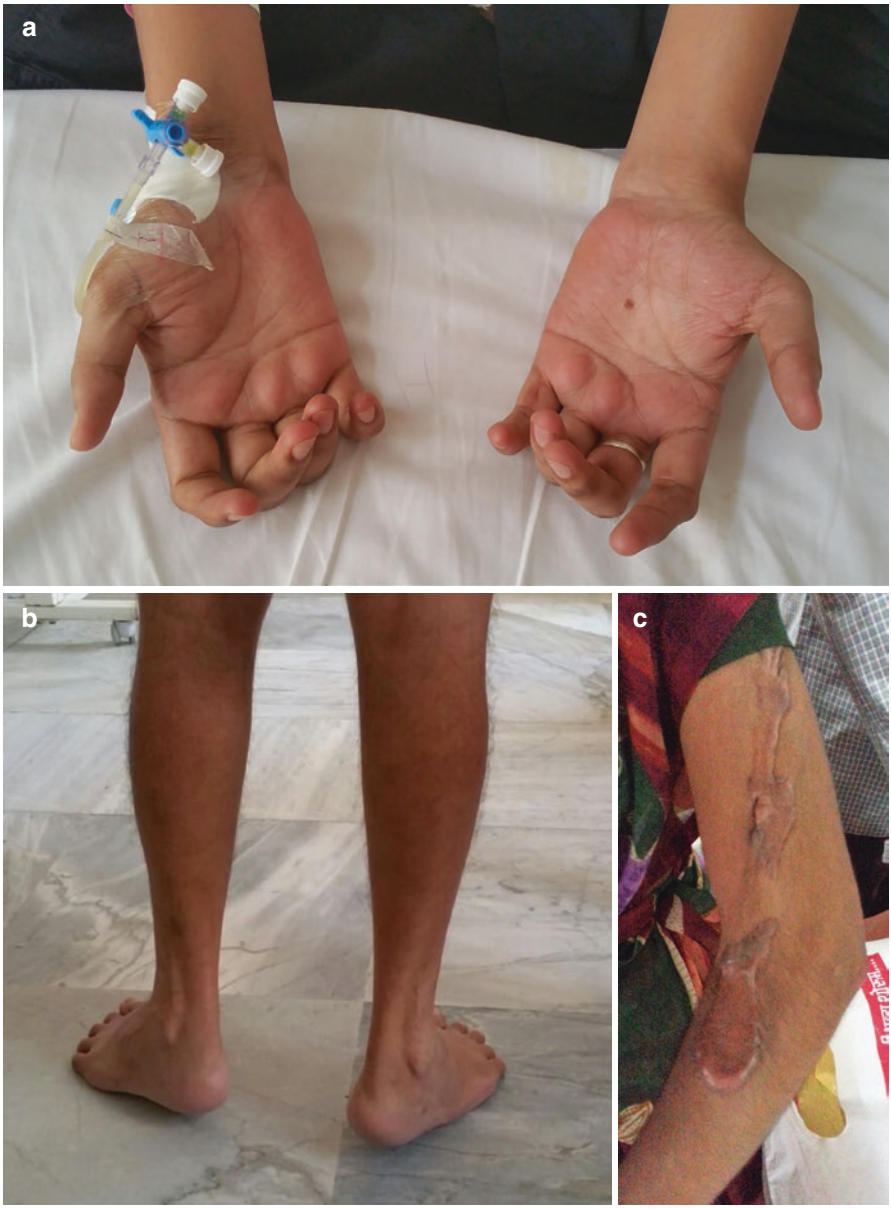

Fig. 14.1 (**a**) Finger contractures, (**b**) ankle contracture and (**c**) keloids over forearm and arm in three different patients with Bethlem myopathy

Fig. 14.1 (continued)

(merosin), a glycoprotein. Collagen VI is one of the major components of this basement membrane. Mutation in gene encoding the laminin 2 and collagen VI causes merosin-deficient CMD (Tome et al. 1994) and Ullrich/Bethlem CMDs (Camacho et al. 2001; Demir et al. 2002; Pan et al. 2003), respectively. Integrins are cell adhesion receptors situated in sarcolemma and link sarcolemma and basement membrane independent of alpha-dystroglycan. Integrin alpha-7/beta-1 is specific for skeletal muscles, and mutation in gene coding them causes rare type of CMDs as described in Table 14.1. Rigid spine syndrome occurs due to mutation in SEPN1 gene coding for selenoprotein N present in endoplasmic reticulum (Petit et al. 2003), which is involved in redox reaction into cell and protecting it from damage.

14.5 Investigations

Salient investigational findings of CMD are tabulated below (Table 14.4).

Table 14.4 Salient laboratory features in CMD

Disorders	Creatine kinase (CK)	Muscle biopsy	MRI brain
Defects of glycosylation			
Muscle–eye–brain disease	2–15 times of normal	Dystrophic features IHC: abnormal glycosylation of α-dystroglycan	Cobblestone lissencephaly
Walker–Warburg syndrome	2–15 times of normal	Dystrophic IHC: decreased α-dystroglycan	Cobblestone lissencephaly
Fukuyama CMD (FCMD)	2–15 times of normal	Dystrophic IHC: decreasedα -dystroglycan	Migration defects
CMD with muscle hypertrophy (MDC1C)	2–75 times of normal	IHC: decreased or absence of α-DG	Normal to structural abnormality
CMD with severe intellectual impairment and abnormal glycosylation (MCD1D)	3–15 times of normal	IHC: decreased α-dystroglycan	Pachygyria, white matter abnormalities, hypoplasia of brainstem
Defects of structural proteins			
UCMD	Normal to 5 times of normal	Dystrophic features EM: complete absence of myofibril IHC: reduced or absent collagen VI	Normal
Bethlem myopathy	Normal to mildly raised	Nonspecific or dystrophic	Normal; MRI muscles show characteristic involvement (Fig. 14.2) (Fu et al. 2016)
Merosin-deficient CMD (MDC1A)	>1000 U/L	Dystrophic features IHC: partial or total laminin α2 deficiency	White matter abnormalities, structural abnormalities of occipital cortex
Integrin α7-deficient CMD	Mild increase	More myopathic than dystrophic IHC: absent integrin alpha-7 subunit	Normal
CMD with joint hyperlaxity	Normal to 5 times of normal	Nonspecific; some shows central nucleus	Normal
CMD with epidermolysis bullosa	>1000 U/L	Nonspecific dystrophic changes with inflammation	Brain atrophy
Proteins of the ER and nucleus			
Rigid spine syndrome	Normal to moderately increased	Nonspecific dystrophic changes	–
LMNA-deficient CMD	Mild to moderate increased	Moderate to severe dystrophic changes	–

Table 14.4 (continued)

Disorders	Creatine kinase (CK)	Muscle biopsy	MRI brain
Others			
CMD with respiratory failure and muscle hypertrophy (MDC1B)	Marked rise	Nonspecific dystrophic changes IHC: secondary laminin α2 deficiency	–

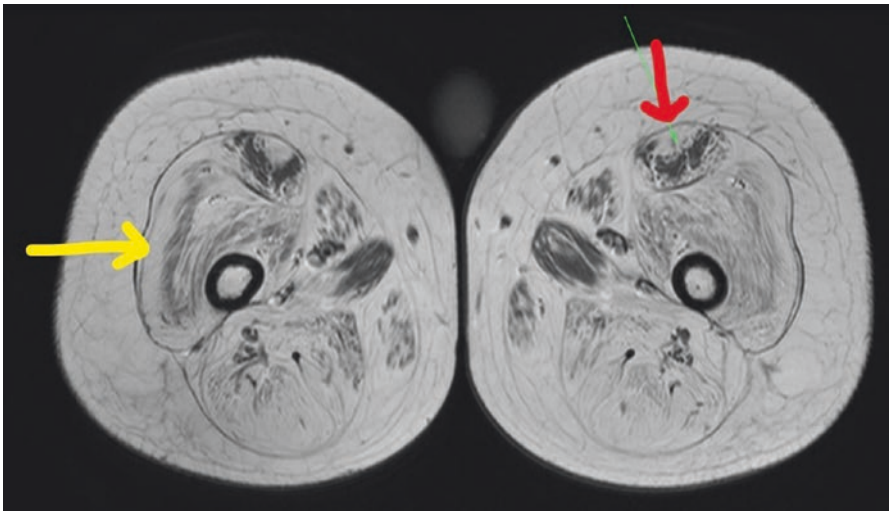

Fig. 14.2 Diffuse peripheral fatty infiltration of vastus lateralis with relative central sparing 'sandwich sign' (*yellow arrow*) and fatty infiltration with atrophy of rectus femoris surrounding a midpoint of fatty infiltration (*red arrow*). (Courtesy Dr. Neha Shah, Bombay hospital, Mumbai)

Recently, imaging of muscles has revealed differential involvement of some group of muscles in patients with CMD (Fig. 14.2).

14.6 Differential Diagnosis

Differentiation should be made from other causes of floppy baby as given in Chap. 10.

14.7 Management

Management of CMDs is palliative; at present no definite treatment is available. Approach should be individualised. Physical therapy, stretching exercises, occupational therapy for maintenance of mobility and prevention of contractures should be promoted. Cane, wheelchairs, orthotics and walker should be given to maintain motility. Orthopaedic correction for foot deformity, contractures and scoliosis can be advised. Respiratory insufficiency needs particular attention; every patient should be subjected to regular respiratory function assessment. Vaccine against the common pathogens and proper use of antibiotics are required, tailored to the local requirements. Nocturnal non-invasive positive pressure ventilation should be implemented whenever needed. Early speech, language and dietary input are necessary. Gastrostomy may be required for feeding difficulties in merosin-deficient CMDs. Anticonvulsant are needed for seizure control. Shunting procedures for hydrocephalus or encephalocele may need to be considered in some patients.

Key Points

When to suspect:

- Early infantile myopathy
- Neuromuscular and non-neuromuscular features (Tables 14.2 and 14.3)
- Elevated CK
- Dystrophic muscle biopsy

How to diagnose:

- Characteristic patterns on MRI
- Muscle biopsy: Immunocytochemistry
- Genetic studies

14.8 Prognosis

In merosin-deficient CMDs, patients are severely disabled and remain dependent for most of their lives. Children with Fukuyama CMDs also remain dependent as they do not attain any independent motor milestone; however slow progressive disease process allows them to achieve adulthood. Walker–Warburg disease is a severe form of CMD, and children die within 2 years of life. Compared to Walker–Warburg disease, muscle eye brain disease is less severe. In Ullrich CMD, clinical severity varies from severe to mild, some patients never achieve walking ability and some may lose it over the time. Bethlem is milder spectrums of the same disease as Ullrich myopathy and patients achieve independence for prolonged periods of time.

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Congenital Myopathies

15

15.1 Introduction

Congenital myopathies are a group of genetic skeletal muscle diseases, which typically present at birth or in early infancy as hypotonia and skeletal muscle weakness with static or slowly progressive clinical course. There are four broad histopathological subtypes of classical congenital myopathies, e.g. nemaline myopathy (rods), central core disease (cores), centronuclear/myotubular myopathy (central nuclei) and congenital fibre-type disproportion (hypotrophy of type 1 fibres) (North et al. 2014). Over the last decade, genetic basis of the different forms of congenital myopathy has been identified. In this chapter we will discuss the key features that are common to all forms of congenital myopathy and specific features that help to differentiate these genetic subtypes.

15.2 Epidemiology

The first report of a congenital myopathy was in 1956 when Shy and Magee described a congenital nonprogressive myopathy with central cores (Shy and Magee 1956). Approximately 10–15% of floppy infants are shown to have congenital myopathies of various types (Fardeau and Tomé 1994). Mutations in RYR1 were the most common cause of congenital myopathies, occurring at 1:90,000 in the United States (Amburgey et al. 2011). A study of 50 patients from South India showed that centronuclear myopathy is most common (Uppin et al. 2013). A small case series of congenital fibre-type disproportion (Sharma et al. 2004) and of nemaline myopathy (Deepti et al. 2007) has been described from India. Patients present in the neonatal or early infantile period, but uncommonly, later presentations well into adulthood have been described. Both sexes are affected equally in most congenital myopathies since inheritance is usually autosomal. In X-linked forms, boys are affected almost exclusively, although occasional female carriers with clinical manifestations have been described.

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15.3 Clinical Features

Congenital myopathies can be analysed according to the clinical features as follows (Table 15.1):

Table 15.1 Inheritance, genes and core clinical features

Disease	Genetics and inheritance	Clinical features
Central core disease	Chromosome 19q12-13.2 RYR1 locus (ryanodine receptor gene locus)—most common mutations in transmembrane domain (AD > AR) (Romero and Clarke 2013)	Decreased foetal movements, breech presentation, delayed motor milestones Severe cases: global hypotonia, weakness of facial muscles, ocular involvement (ptosis and/or ophthalmoplegia) (Romero et al. 2003) Later: proximal muscle weakness, limb girdle pattern (Romero and Clarke 2013) Skeletal malformations: CDH, tendon contractures, pes cavus, pes planus, club foot, scoliosis, severe arthrogryposis, kyphoscoliosis Malignant hyperthermia is an allelic disorder with defect in same gene, responsible for Ca2+ channel function (Lynch et al. 1999)
Nemaline myopathy (NM)	NEB gene (~50% of cases)—AR ACTA1—~25% of cases, AD (90%) > AR (10%) (Ryan et al. 2001) TPM3, TPM2—AD KLHL40 (KBTBD5)—AR CFL2, TNNT1—rare (Agrawal et al. 2007; Johnston et al. 2000)	NM is clinically heterogeneous and can be classified into (1) severe congenital NM, (2) intermediate congenital NM, (3) typical congenital NM, (4) childhood/juvenile-onset NM, (5) adult-onset NM, (6) other atypical forms (ophthalmoplegia, cardiomyopathy) (Wallgren-Pettersson and Laing 2000) Facies—long and narrow, with either prognathous jaw or abnormally short, at birth indistinguishable from congenital myotonic dystrophy ACTA1 mutation more common in severe weakness If able to ambulate before 18 months—good pointer towards survival (Ryan et al. 2001) Large size and repetitive nature of NEB gene is an obstacle to clinical testing Age at presentation and severity of weakness also help in prognostication Nemaline rods can be seen in inflammatory myopathy and late-onset NM with monoclonal gammopathy

Table 15.1 (continued)

Disease	Genetics and inheritance	Clinical features
Myotubular myopathy (a variant of centronuclear myopathy) (Spiro et al. 1966)	MTM1 gene (chromosome X, Xq28) (Laporte et al. 1996)	Decreased foetal movements, polyhydramnios Severe generalised hypotonia from birth, required mechanical ventilation due to respiratory weakness with ptosis and ophthalmoplegia Neonatal form has bad prognosis, life span only a few months Affected males may have associated undescended testes, pyloric stenosis, inguinal hernia Females are usually asymptomatic carriers but can have mild muscle weakness rarely
Autosomal centronuclear myopathy	DNM2 gene (dynamin 2, AD) BIN1 gene (amphiphysin 2, AR) (Nicot et al. 2007)	AD—onset in childhood, delayed milestones, ptosis, ophthalmoplegia, hypotonia and facial weakness with a positive family history (Fig. 15.1) AR—severe than AD disease Clinically heterogeneous, severe phenotype with early-onset weakness is less common
Congenital fibre-type disproportion	ACTA1 gene (Laing et al. 2004) TPM3 gene (Clarke et al. 2008), TPM2 gene (Monnier et al. 2009), RYR1 (Clarke et al. 2010)	Children are floppy at birth, with diffuse weakness of the face and neck. Contractures of Achilles tendon and congenital hip dislocation are common. Strength may improve in the early childhood, but whether it is secondary to child's normal growth is uncertain Accompanying illness are deformities of feet, high-arched palate and kyphoscoliosis If biopsied again at an older age, many patients originally diagnosed at CFTD may show histological features of other congenital myopathies
Multiminicore disease	SEPN1 (selenoprotein N gene) chromosome 1p36 (AR) Less common—RYR1 gene Rarely titin gene (Carmignac et al. 2007)	Axial muscle weakness, respiratory insufficiency, spinal rigidity, scoliosis Mild phenotype—hand and pelvic girdle weakness and hyperlaxity, ptosis and ophthalmoplegia (Ferreiro et al. 2000) RYR1 recessive mutations—external ophthalmoplegia, ptosis, diffuse weakness and wasting, predominant hip girdle involvement (Ferreiro et al. 2002)

(continued)

Table 15.1 (continued)

Disease	Genetics and inheritance	Clinical features
Core rod myopathy	Most common RYR1 gene (AD, AR) Rare: nebulin (Romero et al. 2009), actin (ACTA1) (Jungbluth et al. 2001), KBTBD13 gene (Sambuughin et al. 2010)	Variable symptoms—foetal akinesia to mild phenotype presenting with proximal or distal weakness, tendon contractures, scoliosis and mild ptosis
Congenital myopathy with prominent nuclear internalisation and large and diffuse areas of structural disorganisation	Most common mutation in the RYR1 gene (AR) (Wilmshurst et al. 2010; Bevilacqua et al. 2011)	Congenital hypotonia, delayed motor milestones, facial diplegia, high-arched palate, open mouth, ptosis and ophthalmoplegia Initially thought to be a variant of centronuclear myopathy but now considered a separate subtype of congenital myopathy Initial biopsy may show central and internal nuclei, but areas of structural disorganisation appear later in the clinical course

The term centronuclear myopathy includes a group of disorders which have in common the histopathological finding of the presence of fibres with internal nuclei. It includes myotubular myopathy, autosomal forms of centronuclear myopathy and late-onset 'necklace' fibre MTM1-related centronuclear myopathy

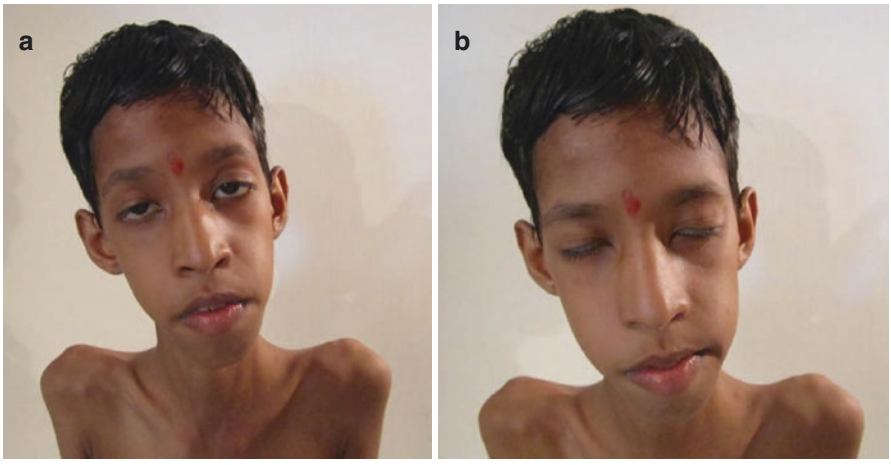

Fig. 15.1 (**a**) Ptosis and (**b**) facial weakness in a patient with centronuclear myopathy

15.4 Pathophysiology (Ravenscroft et al. 2015)

Congenital myopathies result from mutations of contractile, structural and other proteins, which produce structural abnormalities of myofibres and accumulation of abnormal proteins in the sarcoplasm. Five key pathophysiological themes have emerged—defects:

- Sarcolemmal and intracellular membrane remodelling and excitation–contraction coupling: This is crucial to a number of biological processes and membrane repair. A number of genes found to underlie congenital myopathies are involved in such membrane remodelling and excitation–contraction coupling (amphiphysin 2, dynamin 2, myotubularin and myotubularin-related protein 14).
- Mitochondrial distribution and function: Abnormal accumulations, localisation and ultrastructure of mitochondria have been reported, which are characterised by the presence of cores or core-like regions within myofibres.
- Myofibrillar force generation: Defects in genes encoding thin filament proteins or proteins interacting or regulating such proteins result in defect of myofibrillar force generation.
- Atrophy: In congenital myopathies, a common histological abnormality is type I myofibre atrophy indicating the role of skeletal muscle protein synthesis and degradation.
- Autophagy: Impaired autophagy and excessive autophagy can result in skeletal muscle disease. Autophagy has been studied in centronuclear myopathy and is believed to be a direct consequence of the underlying genetic defect.

15.5 Investigations

Muscle biopsy plays an important role in diagnosis of congenital myopathies (Jain et al. 2008). Muscle MRI can help in prioritising one form of congenital myopathy over the other. Key findings are described in Table 15.2.

15.6 Differential Diagnosis

Differential diagnosis of congenital myopathy is similar to that of a floppy infant. Please refer to Chap. 10 for causes of floppy infant.

Table 15.2 Investigative features in congenital myopathies

Diseases	Muscle biopsy light microscopy	Muscle biopsy electron microscopy	MRI of muscles
Central core disease	Cores appear as well-defined lesions of central (uncommonly eccentric) reduced activity on oxidative enzyme reaction with complete type 1 fibre predominance, extend full length of the fibres	Structured cores appear as poorly aligned sarcomere with reduced mitochondria and glycogen; unstructured cores have disorganised sarcomeres and absent mitochondria	Sparing of the rectus femoris, adductor longus, gracilis and hamstring in the thigh; involvement of soleus, gastrocnemius lateralis and peronei; and sparing of the TA, TP and medial head of gastrocnemius (Jungbluth et al. 2004a, b)
Nemaline myopathy	Type 1 fibre predominance, selective atrophy of type 1 fibres and deficiency of type 2B fibres Characteristic nemaline rods appear as subsarcolemmal clusters of red staining bodies (on modified Gomori trichrome)	Nemaline rods appear as subsarcolemmal, dense, osmiophilic bodies A pathological clue for TPM3 is presence of rods only in type 1 muscle fibres (as α-tropomyosin not expressed in type 2 fibres)	In patients with early distal involvement, MRI may show preservation of thigh muscles and early involvement of the tibialis anterior and soleus (Jungbluth et al. 2004a, b)
Myotubular myopathy	High numbers of muscle fibres with central nuclei (which resemble myotubes) With oxidative enzyme reaction, many fibres have darkly staining central spot with a peripheral halo	Central areas of the fibres are occupied by aggregated mitochondria and glycogen particles; myofilaments are seen only in the periphery	No specific pattern
Autosomal centronuclear myopathy	Triad of morphological features in DNM2—radiating sarcoplasmic strands, increased central nuclei and type 1 fibre predominance and hypertrophy. Central area reacts strongly to PAS, and with oxidative enzyme reaction, fibres show spoke-like appearance due to radial arrangement of sarcoplasmic strands (Romero and Clarke 2013)	Centrally placed nuclei, with mitochondria, endoplasmic reticulum, Golgi complex and glycogen particles seen in perinuclear region In sarcoplasmic strands, myofibrils become progressively smaller from periphery to central zone (Fardeau and Tomé 1994; Romero and Bitoun 2011)	In DNM-related dominant centronuclear myopathy, the thigh is diffusely affected with predominant involvement of the rectus femoris and adductor longus. In the lower leg, there is diffuse involvement of all muscle groups with relative preservation of the tibialis posterior
Congenital fibre-type disproportion	Type 1 fibres are consistently and significantly smaller (hypotrophic) than type 2 fibres (Clarke and North 2003) Type 1 fibre hypotrophy can also be seen in metabolic myopathies, neonatal form of myotonic dystrophy	Type 1 fibre hypotrophy with predominance as compared to type 2 fibres	No specific pattern

Table 15.2 (continued)

Diseases	Muscle biopsy light microscopy	Muscle biopsy electron microscopy	MRI of muscles
Multiminicore disease	Focal, poorly delineated zones of diminished oxidative enzyme activity. Smaller and do not extend full length of the fibre, multiple within one fibre	Small areas of Z-line streaming and myofibrillar disruption extending a small number of sarcomeres	No specific pattern
Core-rod myopathy	Muscle fibres show well-delineated cores and cluster of rods in different locations in the same muscle	Cores—central part of the fibre as areas of sarcomeric disorganisation, with decreased mitochondria, rods—subsarcolemmal region	No specific pattern
Congenital myopathy with prominent nuclear internalisation and large and diffuse areas of structural disorganisation	Biopsy in the early stage may show fibre size variation, nuclear internalisation and centralisation with increased endomysial connective tissue. Later stage—large delimited areas with reduced oxidative reaction corresponding with regions of myofibrillar disorganisation		No specific pattern

15.7 Management

Patients with severe early-onset congenital myopathy require prompt ventilator support and gastric feeding through nasogastric tube. Associated illnesses like pyloric stenosis and undescended testes may require immediate attention. Childhood-onset congenital myopathies require correction of skeletal deformities. It is imperative to encourage the child to participate in play therapy, with the aim of increasing motor activity. The importance of referral to physical and occupational therapists cannot be overstated.

15.8 Prognosis

Severe forms of congenital myopathy having respiratory weakness at birth have grave prognosis. Such patients usually succumb to complications related to mechanical ventilation. Patients having childhood-onset congenital myopathy have delayed motor milestones but a nonprogressive disease and are able to manage themselves with some limitations. Adult-onset congenital myopathies may have slowly progressive illness.

Key Points

When to suspect

- Early-onset (usually at birth) muscle weakness
- Nonprogressive
- Familial
- Core clinical features (Table 15.1)

How to investigate

- Variable CK elevation
- Specific muscle biopsy features (Table 15.2)
- Genetics

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Emery–Dreifuss Muscular Dystrophy 16

16.1 Introduction

Emery–Dreifuss muscular dystrophy (EDMD) is an uncommon muscular dystrophy with a characteristic phenotype, which consists of a triad of early contractures, slowly progressive muscle weakness which begins in humero-peroneal distribution and cardiac involvement in the form of conduction defects, arrhythmias and dilated cardiomyopathy. EDMD was initially described by Dreifuss and Hogan in a family living in the coal mine at Appalachian Plateau area of Buchanan County, who were initially believed to be in the BMD spectrum as the transmission was X-linked recessive (Dreifuss and Hogan 1961). Later on Emery and Dreifuss differentiated this dystrophy as a distinct disease (Emery and Dreifuss 1966). Autosomal dominant form of EDMD was recognised in the early 1980s.

16.2 Epidemiology

Limited data exists regarding prevalence of EDMD. The prevalence of XL-EDMD has been estimated to be 1:100,000. Recently, the prevalence of EDMD was reported as 0.13–0.20:100,000 (Norwood et al. 2009). Older studies (Hopkins and Warren 1992) probably overestimated EDMD, considering it to be the third most prevalent muscular dystrophy, following Duchenne and Becker muscular dystrophies.

16.3 Clinical Features

Emery–Dreifuss muscular dystrophy (EDMD) is characterised by a clinical trial.

- Gradually progressive muscle weakness, initially in humero-peroneal pattern with wasting of biceps and triceps and preservation of deltoid muscles. In the lower limbs, ankle dorsiflexion weakness comes early and then extends to the scapular and pelvic girdle muscles (Bonne et al. 2000).

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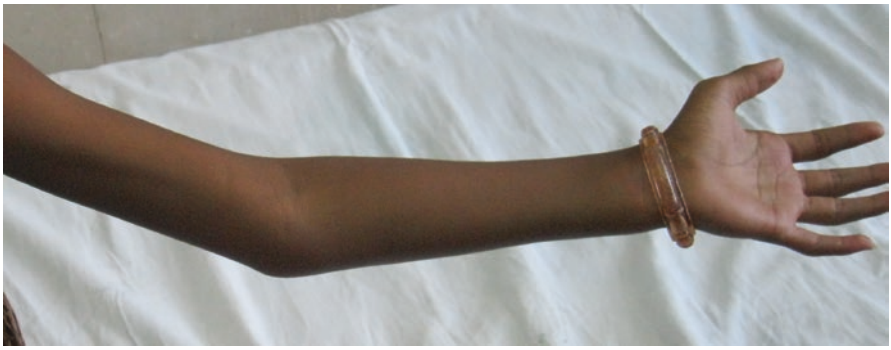

Fig. 16.1 Elbow contractures in autosomal EDMD in a girl

- Joint contractures begin in early childhood, involving the elbow flexors, ankle plantar flexors and spine. Inability to extend elbows completely and early toe walking rigid spine are diagnostic clues (Fig. 16.1) (Bonne et al. 2000).
- Cardiac involvement usually occurs by fourth decade and presents as palpitations, presyncope and syncope, poor exercise tolerance and congestive heart failure, bradyarrhythmias or tachyarrhythmias and dilated cardiomyopathy (Sanna et al. 2003).

Inter- and intrafamilial variability in age of onset, severity and progression of the muscle and cardiac involvement is well known (Mercuri et al. 2000).

16.4 Pathophysiology

Three major groups of proteins have been linked to the pathophysiology of EDMD. Emerin and FHL1 cause X-linked EDMD, while lamin A/C is abnormal in autosomal dominant and recessive EDMD. These proteins share a common location at the nuclear membrane and hence together are known as 'nuclear envelopathies'. These proteins are ubiquitously expressed, but disease manifestations are tissue specific, for unclear reasons. Two pathophysiological hypotheses have been proposed. The first states that disruption of the inner nuclear membrane and the nuclear lamina results in disorganisation of nuclear chromatin and gene expression. The second states that the disruption of mechanical strength of the cell nucleus leads to weakening of nuclear lamina, which leads to structural and signalling defects in tissues facing mechanically stress such as muscle and heart.

16.5 Diagnosis

Clinical diagnosis is mainly based on clinical findings of classical triad and family history. Electrophysiology usually shows myopathic features with normal nerve conduction studies, but neuropathic patterns can be seen in X-linked EDMD. MRI

of muscle shows a diffuse pattern of involvement of various muscles, e.g. biceps, soleus, peronei, vasti, glutei and paravertebral muscles. Serum CK concentration is normal or moderately elevated (2–20× upper normal level), being maximum in the initial stages of the disease. Routine histology of the muscles may not give diagnostic clues besides showing nonspecific myopathic changes, but immunocytochemistry can show important changes in the staining patterns of emerin, FHL1 or laminin. Western blotting is more reliable than qualitative staining. Molecular testing approaches include serial single-gene testing, multigene panel and genomic testing. The approach can be based on the status of emerin and the pattern of inheritance in a given family.

16.6 Differential Diagnosis

Other muscle diseases can present with combination of weakness and joint contractures and need to be differentiated from EDMD (Table 16.1).

16.7 Management

Patients need to be regularly monitored for cardiogram, Holter monitoring, echocardiography and evaluation of respiratory function by chest X-ray, ABG and vital capacity measurements. Metabolic functions like glycaemia, insulinemia and

Table 16.1 Differential diagnosis of EDMD with their key differentiating features

Diseases	Key differentiating features	Mode of inheritance
Limb–girdle muscular dystrophies with cardiac involvement	Absence of joint contractures Later onset of illness Lower girdle weakness in most types	AD/AR
Facioscapulohumeral muscular dystrophy	Typical clinical pattern of weakness, absence of joint contractures and cardiac disease	AD
Scapuloperoneal syndromes	Absence of joint contractures and cardiac disease	AD/AR
Rigid spine syndrome	Early respiratory failure No cardiac disease	AR
Collagen type VI-related Bethlem myopathy	Absence of cardiac disease; specific muscle imaging pattern	AD
Dystrophinopathies	Absence of joint contractures in the upper limbs	XL
Pompe disease	Absence of joint contractures; specific muscle pathology (PAS positive vacuoles)	AR
Ankylosing spondylitis	No muscle weakness	Acquired

triglyceridemia need a watch in cases where LMNA gene is abnormal (Garg et al. 2002; van der Kooi et al. 2002).

Physical therapy and stretching exercises help in preventing development of contractures. Cardiac management depends upon symptoms and needs to be targeted towards arrhythmias (antiarrhythmic drugs, cardiac pacemaker and defibrillator) and for congestive heart failure pharmacologic (diuretics, ACE inhibitors), and non-pharmacologic therapy can be used (Bécane et al. 2000; Bonne et al. 2003 and Boriani et al. 2003). Respiratory assistance in the form of assisted coughing techniques and non-invasive or invasive ventilation may become necessary in later stages of the disease. Surgery for the release of contractures and for scoliosis can improve mobility in carefully selected patients. Mechanical aids for support can prolong ambulation.

16.8 Prognosis

The age of onset, severity and progression of EDMD can vary greatly in different individuals with EDMD, even amongst affected members of the same family. Some experience childhood onset with rapid disease progression and severe complications, whereas others can have adult onset and slowly progressive course. Muscle weakness and atrophy are usually slowly progressive during the first three decades of life but can become more rapid later (Bonne et al.). Some individuals with autosomal dominant EDMD may become wheelchair bound as the disease advances, unlike X-linked EDMD where loss of ambulation is rare. Although onset can vary, heart abnormalities usually develop after the second decade of life. Affected individuals may develop cardiomyopathy and heart block which can result in sudden deaths but can be prevented with timely intervention (Bonne et al. 2004 and http://ghr.nlm.nih.gov/condition/emery-dreifuss-muscular-dystrophy 2006).

Key Points

When to suspect

- Early contractures
- Cardiac involvement
- X-linked (sometimes autosomal) transmission

How to diagnose

- Clinical triad
- ECG, Holter, 2D Echo
- Immunocytochemistry and Western blotting of the muscle tissue
- Genetic studies

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Oculopharyngeal Muscular Dystrophy 17

17.1 Introduction

OPMD is a late-onset, dominantly inherited disorder of the muscle. It is associated with progressive eyelid ptosis, dysarthria, dysphagia and proximal weakness (Abu-Baker and Rouleau 2007). The disorder was described in a cohort of Canadian and Spanish-American population, but now it is increasingly well recognised worldwide. The disease is caused by mutations in the polyadenylate-binding protein nuclear 1 (PABPN1) (Isenberg and Kahn 1981). The cardinal pathologic findings of OPMD are the presence of distinctive muscle fibres containing rimmed vacuoles under a light microscope (LM) and of unique myocyte nuclei containing tubulofilamentous inclusion under an electron microscope (EM) (Tomé et al. 1997a, b). Treatment largely remains supportive as in other muscular dystrophies.

17.2 Epidemiology

In 1915, Taylor reported a French-Canadian family of progressive dysphagia with ptosis (Taylor 1915). In 1962, Victor et al. introduced the term oculopharyngeal muscular dystrophy and gave a detailed account of a North American Jewish family of eastern European origin (Victor et al. 1962). The disease has an uneven geographical distribution, although now recognised worldwide. The prevalence of OPMD ranges from 0.5 to 1/100,000 population in European countries (Maksimova et al. 2008), 1/1000 French Canadians in Quebec (Brais et al. 1999) and 1/600 in Israel's Bukharan Jews emigrating from Central Asia (Blumen et al. 1997). The incidence of OPMD may be lower or underestimated among Asian and African ethnicities, as only a few reports have been published (Xu 1985; Sarkar et al. 1995).

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17.3 Clinical Features

Weakness starts insidiously and manifests in the fifth or sixth decade, with a slowly progressive course; most sufferers are symptomatic by the age of 70 years (Rüegg et al. 2005; Brais 2003). Ptosis is seen in 100% cases by 60 years of age, is always bilateral, but may be asymmetrical. Swallowing difficulty remains a constant feature due to weakness of the levator palpebrae and pharyngeal muscles. Although other extraocular muscles may become gradually involved, complete external ophthalmoplegia is rare, and intrinsic eye (ciliary, sphincter) muscles are not affected (Tomé and Fardeau 1994). Patients begin to experience difficulty in swallowing solid foods. Later on, fluids become difficult to swallow as well. The rest of the facial musculature is spared till late stages. However, weakness and atrophy of the tongue can be observed in a large proportion of patients (Bouchard et al. 1997). Dysphonia is reported in 50% of the cases, and weakness of the pelvic musculature is seen in early stages of the disease. The muscle involvement is symmetric, and its severity, in descending order is levator palpebrae, tongue, pharynx, extraocular muscles, iliopsoas, adductor femoris, gluteus maximus, deltoid and hamstrings (Little and Perl 1982).

Disease progression varies from one individual to another. Complications include choking, regurgitation, aspiration and pneumonia (Little and Perl 1982). Consecutive aspiration pneumonia, together with malnutrition or starvation, is the leading cause of death in patients with OPMD. These events do not seem to shorten the life expectancy but have an impact on the quality of life and during the last years of life. A small number of patients (10%) take to wheelchair due to a combination of limb weakness and cachexia (Bouchard et al. 1997; Brais et al. 1999).

17.4 Pathophysiology

OPMD is inherited as an autosomal dominant trait with complete penetrance and without gender preference. The OPMD locus maps to chromosome 14q11.2–q13 by linkage analysis (Brais et al. 1995). There are expansions of the short (GCG) trinucleotide repeat in the coding sequence of the poly(A) binding protein nuclear 1 (PABPN1, also known as PABP2) gene (Brais et al. 1998). The expansion of GCG repeats is believed to result in abnormal folding of the polyalanine domains of PAPBN1. The misfolded proteins are resistant to degradation and accumulate as the intranuclear inclusions seen on electron microscopy. Although OPMD is caused by triplet expansions, there is no correlation between expansion size and onset or severity of disease. Unlike many other triplet expansion diseases, the mutation is quite stable over generations and does not lead to clinical anticipation.

17.5 Investigations

Genetic studies are now recommended as a first-line diagnostic method. The test has 99% sensitivity and specificity (Brais et al. 1998). Muscle biopsy is no longer essential for the diagnosis of OPMD but can provide helpful information in clinically

atypical cases. The creatine kinase (CK) levels may be normal or elevated two to three times than normal. Electromyography may show both myogenic and neurogenic MUPs with absence of spontaneous activity.

The histology of OPMD muscle biopsy specimens shows rimmed vacuoles within the muscle fibres which most probably derive from an autophagic process (similar vacuoles are seen in inclusion body myositis). Small numbers of angulated fibres are also seen, which may represent a concomitant denervation process linked to ageing. Electron microscopy reveals tubulofilamentous inclusions of about 8.5 nm in diameter within the nuclei of muscle fibres and forms the most specific diagnostic feature of OPMD (Tomé et al. 1997a, b). These inclusions consist of the mutated, aggregated PABPN1. Dysphagia can be assessed by barium studies.

17.6 Differential Diagnosis

Some diseases can have isolated extraocular or bulbar involvement or both. These diseases form close differentials of OPMD. Their salient clinical and investigational features have been summarised below (Table 17.1).

Table 17.1 Differential diagnosis of OPMD with their key distinguishing features

Diseases	Key distinguishing features
Myasthenia gravis	Subacute onset, diurnal variation and fluctuations in symptoms. Family history is negative except in CMS variety. Examination shows marked fatigability, improvement on ice pack application and significant decremental response on RNS study
Chronic progressive external ophthalmoplegia (CPEO)	Slowly progressive, symmetrical ptosis, early slowing of saccades and marked ophthalmoparesis. Dysphagia is less prominent. Associated features are retinal degeneration, ataxia and cardiac involvement are seen in CPEO
Kearns – Sayre syndrome	Sporadic, symptom onset before 20 years and additional features of pigmentary retinopathy, seizures, and deafness helps in differentiation
Myotonic dystrophy	Characteristic muscle wasting and weakness, cataract, cardiac involvement, systemic features and electrophysiological features of myopathy
Congenital myasthenic syndrome (CMS)	First to second decade onset, ptosis, ophthalmoparesis, recurrent episodes of bulbar and respiratory weakness, affection of family members, absence of AchR and lack of response to acetylcholine esterase inhibitors favour CMS
Multiple cranial neuropathies	Weakness in distribution of cranial nerves, pupillary involvement, absence of family history
Lambert-Eaton myasthenic syndrome (LEMS)	Mild and less common ocular and bulbar involvement, prominent limb weakness at onset, pain in limbs, autonomic dysfunction, sensory complaints, transient improvement with exercise, depressed reflexes, more than 100% increment on RNS and presence of tumours such as small cell lung carcinoma favour LEMS
Amyotrophic lateral sclerosis	Bulbar onset ALS is a close differential diagnosis. Absence of ptosis, tongue atrophy with fasciculations, sparing of extraocular muscles, presence of jaw jerk, exaggerated gag reflex and pseudobulbar affect point to bulbar onset ALS

17.7 Management

17.7.1 Surgical Correction of Ptosis

Correction is considered when ptosis interferes with vision or compensatory neck posture becomes painful. The resection of levator palpebrae aponeurosis or frontal suspension of the eyelids may be performed (Rodrigue and Molgat 1997). Marked ophthalmoplegia is a relative contraindication, and intermittent use of glasses with eyelid props can improve this situation.

17.7.2 Management of Dysphagia

Dietary modifications like swallowing small pieces of foods, thickening liquids and eating slowly can be advised. Surgical correction of dysphagia is indicated when dysphagia becomes severe and leads to weight loss or recurrent pneumonia. Cricopharyngeal myotomy helps to relieve the functional obstruction (Duranceau 1997). Severe dysphonia and lower oesophageal sphincter incompetence are contraindications for the procedure. Alternatively, upper oesophageal sphincter dilation using endoscopy may be considered as it is less invasive and does not require general anaesthesia (Mathieu et al. 1997).

17.7.3 Newer Advances in Treatment

Doxycycline (anti-aggregation and anti-apoptotic) was shown impressive results in transgenic mouse models (Davies et al. 2005).

17.8 Prognosis

The life expectancy is not affected in OPMD but the quality of life has serious impact (Muscular Dystrophy UK 2016). The dysphagia becomes worrisome with time and needs advanced medical and surgical management. The malnutrition related to dysphagia needs dietary counselling periodically. The major threat to life with aspiration pneumonia should be well explained to patient and caretaker.

Key Points

When to suspect

- Late onset of bilateral ptosis, dysphagia and dysarthria
- Autosomal dominant

How to investigate

- Elevated CK
- Histology showing rimmed vacuoles and tubulofilamentous nuclear inclusions
- GCG trinucleotide repeats

How to treat

- Supportive therapy

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Part III

Symmetric Distal Weakness

Myotonic Dystrophies

18

18.1 Introduction

Myotonia is characterised by delayed relaxation of muscles after sustained voluntary contraction. Amongst myotonic disorders, myotonic dystrophy (DM) is the most common. DM is an autosomal dominant disorder. It is a multisystem disorder affecting the muscles, ocular lens, heart, endocrine organs and gastrointestinal and central nervous system in varying proportions. There are of two types: DM 1 and DM 2. DM 1 is caused by expansion of CTG repeats in myotonic dystrophy protein kinase (DMPK) gene, and DM 2 is caused by CCTG expansion in zinc finger protein 9 (ZFN9) gene. Besides these two myotonic dystrophies, nondystrophic myotonias are also encountered, which are caused by chloride and sodium channel mutations. It is important to differentiate between myotonic dystrophy and nondystrophic myotonias, as they differ in management and prognosis. This chapter will deal with DM 1 and DM 2.

18.2 Epidemiology

The prevalence of DM 1 varies in different ethnic populations of the world. This diversity is due to difference in number of CTG alleles in normal individuals of different ethnicity (Basu et al. 2001). The frequency of large-sized normal alleles correlates with the prevalence of DM 1, and both are highest in Western Europe and Japanese populations, lower in Southeast Asians and lowest in sub-Saharan Africans (Tishkoff et al. 1998). Its prevalence varies widely, from 1/475 in certain regions of Canada (Bouchard et al. 1989), 2–5.5/100,000 in European populations (Tishkoff et al. 1998), 1/20,000 in Japanese (Osame and Fursho 1983) to virtual absence in sub-Saharan Africa (Goldma and Ramsay 1994). There are extensive variations in frequencies of normal alleles in Indian populations ranging from 5–31 repeats in caste populations to 5–23 repeats in tribal populations (Basu et al. 2001). Similarly, prevalence of DM 2 varies with populations in different continents (Mankodi 2008).

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18.3 Clinical Features

18.3.1 DM 1

DM 1 is a multisystem disorder with wide spectrum of presentations ranging from severe illness at birth to mild weakness and cataract in adults. Also, there are variations in severity of involvement of multiple organs. Clinical examination of apparently normal family members is often helpful in this autosomal dominant disease. Examination is particularly relevant as the manifestations are varied and involvements are of multiple systems; hence the family may not associate the protean manifestations to a single causation and may choose not to report them. Based on age at onset, CTG repeats and severity of illness, DM 1 has been divided into the following subtypes.

18.3.1.1 Congenital DM 1 (CDM)

It is the most severe form which presents prenatally as reduced foetal movements and polyhydramnios. At birth, patients present with neonatal hypotonia, facial diplegia, tented upper lip and bulbar and respiratory weakness. They are also mentally retarded. The number of CTG repeats is more than 1000. Those who survive childhood gradually improve and achieve developmental milestones (Udd and Krahe 2012; Thornton 2014).

18.3.1.2 Classical DM 1

It is the most common form of DM 1. The number of CTG repeats varies from 50 to 1000 repeats. Symptoms begin in adolescence or adulthood (Turner and Hilton-Jones 2014). Clinical picture is dominated by myotonia and characteristic features of muscle wasting and weakness. Myotonia can be demonstrated during action (finger grip, eye closure, jaw opening) and on percussion of muscles (thenar eminence, wrist extensors, tongue). Myotonia improves with muscle activity 'warm-up phenomenon' and worsens with rest and cold exposure. The characteristic features of myotonic myopathy are ptosis, wasting and weakness of temporalis, masseter, facial muscles and sternocleidomastoid which give rise to 'hatchet face' and 'swan neck' appearance (Fig. 18.1). Bulbar muscles and neck flexors are involved quite early in the illness (Mankodi 2008; Turner and Hilton-Jones 2014). Patients have wasting and weakness of the forearm with relative sparing of arm and shoulder girdle which gives an appearance like a shank of an animal (Pradhan 2007). In lower limbs, ankle dorsiflexors and quadriceps are relatively more affected than gastrocnemius, hamstrings and pelvic girdle muscles (Turner and Hilton-Jones 2010; Mankodi 2008; Thornton 2014). Respiratory muscle weakness can present as exertional dyspnoea and excessive daytime sleepiness (Shahrizaila et al. 2006). Uncommonly reported features are true hypertrophy of calf muscles and muscular pain (Thornton 2014). DM 1 also involves multiple organs as listed in Table 18.1.

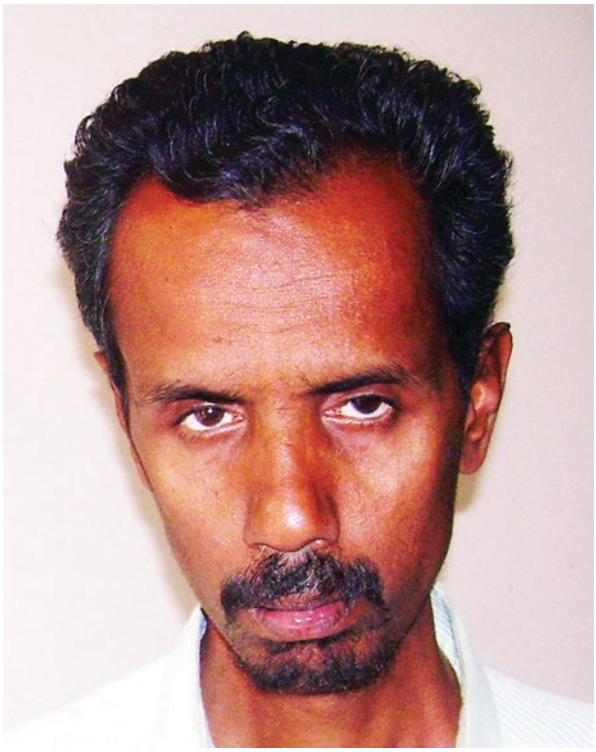

Fig. 18.1 Mild ptosis, hatchet face and thin neck in a patient with DM1

Table 18.1 Systemic manifestations in DM 1

Affected organs	Presenting features
Heart	PR prolongation, atrioventricular block, atrial tachycardia, risk of ventricular tachycardia and later-stage, left ventricular dysfunction. Patients are at risk of sudden cardiac death
Eyes	Premature cataracts (Christmas tree-like appearance)
Central nervous system	Behavioural and cognitive changes like apathy, executive dysfunction, memory disturbance and altered sleep habits. They may explain functional disabilities which are out of proportion to their muscle weakness
Endocrine system	Testicular atrophy, balding, erectile dysfunction and insulin resistance
Gastrointestinal tract and liver	Constipation, gall bladder stones, elevated liver enzymes and dyslipidemia
Cancer	For unknown reasons, DM 1 patients are at risk of cancer of thyroid gland, ovary, choroidal melanoma

(Mankodi 2008; Thornton 2014; Bird 2015)

18.3.1.3 Mild DM 1

Patients with CTG repeats in the range of 50–150 present later in life, often after 40 years of age. They have mild weakness, myotonia and cataracts (Kamsteeg et al. 2012; Turner and Hilton-Jones 2014; Thornton 2014).

18.3.2 DM 2

The multisystem nature of DM 2 is generally similar to DM 1. However, the following features occur in DM 2 which helps to differentiate from DM 1: later age of onset; absence of congenital form; muscle pain and stiffness as presenting complaint; prominent proximal weakness; milder wasting; lesser severity of facial, bulbar weakness; presence of calf hypertrophy; and lesser impairment of cognitive functions (Day et al. 2003; Udd and Krahe 2012).

18.4 Pathophysiology

18.4.1 DM 1

The number of normal CTG repeats in DMPK gene is variable and ranges from 5 to 37 repeats. Patients with DM 1 have more than 50 CTG repeats in 3′ noncoding region of DMPK gene located on chromosome 19. Patients with 38 to 49 repeats are asymptomatic, but their children are at risk of having larger number of repeats. Hence, these are known as permutation alleles (Turner and Hilton-Jones 2010; Thornton 2014). Leucocyte DNA correlates poorly with severity of illness as somatic mosaicism occurs within each organ probably due to changes in DNA repair mechanisms. Hence, in patients with large CTG repeats, they may be stable in leukocyte DNA but unstable in other tissues like the muscle and heart. This phenomenon also explains variations in disease severity within different organs (Turner and Hilton-Jones 2014). The mutant DMPK mRNA affects RNA splicing of other muscle chloride ion channels, thus resulting in myotonia. The severity of illness and age of onset depends on number of CTG repeats. Milder expansion of repeats (50–150) manifests at later age, and the associated illness is mild in nature. Larger expansion >1000 repeats are associated with severe illness at birth (Turner and Hilton-Jones 2014).

18.4.2 DM 2

The number of normal CCTG repeats in intron 1 of ZFN 9 gene on chromosome 3 is 10–33. In DM 2, the number of repeat expansions is more than 75. Molecular mechanisms similar to RNA splicing abnormalities in DM 1 occur in DM 2. Unlike DM 1, correlation between number of repeats and disease onset and severity is poor (Day et al. 2003; Turner and Hilton-Jones 2014).

18.5 Investigations

18.5.1 DM 1

Electrocardiogram shows prolongation of P-R interval, AV block and atrial and ventricular arrhythmias. Slit lamp examination should be done to look for cataract. Creatine kinase (CK) levels may be normal or modestly elevated. Serum glucose, lipid profile and liver enzymes can be deranged. Needle electrode examination shows myopathic potentials, myotonic discharges and early recruitment (Fig. 18.2). Short exercise test may show transient drop in compound muscle action potentials (Thornton 2014). In a study, prevalence of peripheral neuropathy was found to be 17% in DM 1 (Hermans et al. 2011). MRI brain shows temporo-polar and periventricular white matter changes in some patients (Di Costanzo et al. 2002). Definitive diagnosis is established by detection of more than 50 CTG repeats in the 3′ noncoding region of DMPK gene. Conventional PCR can detect a lower range of CTG repeats and thus can identify the normal and premutated alleles. Triplet-primed PCR (TP-PCR) is able to detect large pathogenic CTG repeat, capable of differentiating normal, premutated and fully mutated alleles of DMPK gene, thus forming an efficient screening method in the clinical diagnosis of DM 1. Southern blot has been the gold standard for the detection of DMPK alleles containing 100 CTG repeat units but is time consuming (Fig. 18.2) (Kamsteeg et al. 2012; Kumar et al. 2014).

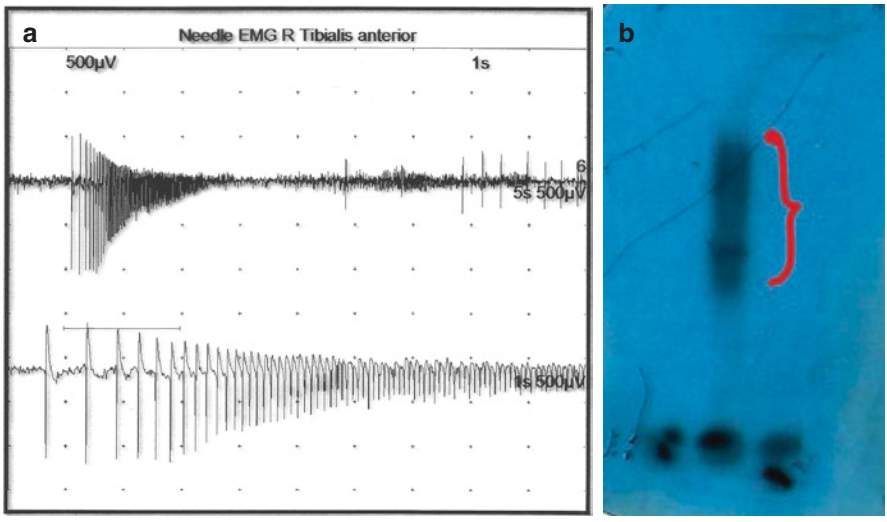

Fig. 18.2 (**a**) Myotonic discharges; top trace: At a sweep speed of 3 s, the waxing and waning pattern in amplitude and frequency. Bottom trace shows the individual discharge. (**b**) Detection of DMPK CTG repeat expansion by Southern blot analysis; Lanes 1 and 3: Normal individuals with no CTG repeat expansion in DMPK gene; Lane 2: Affected DM 1 individual with expanded CTG repeats in DMPK gene (Courtesy Dr. Sushant Chavan, Progenex laboratory, Mumbai)

18.5.2 DM 2

Definitive diagnosis is established by detection of more than 75 CCTG repeats in ZFN 9 gene. The number of repeat units can range from 75 to 11,000 with a mean of 5000. As in DM 1, exact number of repeats can only be determined by DNA sequencing (Kamsteeg et al. 2012). Other investigations are similar to DM 1, but frequency of abnormalities is lesser than in DM 1 (Finsterer 2002; Day et al. 2003).

18.6 Differential Diagnosis

The phenotype of DM 1 comprises of characteristic wasting, weakness, myotonia and systemic features. Combination of these features is rarely found in other diseases. However, some conditions can resemble DM 1 phenotype and needs to be differentiated from DM 1 (Table 18.2).

DM 2 has prominent limb–girdle weakness and needs to be differentiated from inflammatory myopathy and limb–girdle muscular dystrophy. Combination of ptosis, facial, bulbar weakness, myotonia and systemic features help in differentiation.

Table 18.2 Differential diagnosis of DM and their key differentiating features

Differentials of myotonic disorders	Diseases	Key differentiating features
	Myotonia congenita (MC)	Early-onset, prominent myotonic symptoms rather than weakness, normal cognition and no systemic features. Significant decrement on short exercise testing
	Paramyotonia congenita	Prominent myotonia of the eyelids and jaw, no weakness and most importantly worsens with muscle activity and in response to cold temperature
	Hypothyroid myopathy	These patients may not have systemic features of hypothyroidism. Apart from electrophysiological evidence of myotonia, these patients have characteristic myo-oedema and highly elevated CK values
Differentials of ptosis, facial, bulbar and limb weakness	Myasthenia gravis	Subacute, fluctuating course, signs of fatigability, absence of diplopia, negative family history, significant decrement on repetitive nerve stimulation and absence of systemic features.
	Mitochondrial myopathy	Vision diminution due to pigmentary retinopathy and optic atrophy rather than cataract, short stature, impairment of extraocular movements and peripheral neuropathy
	Oculopharyngeal muscular dystrophy	Fourth to fifth decade onset of impairment of extraocular movements, proximal limb weakness and absence of cardiac involvement and cognitive decline

18.7 Management

At present, no definitive therapy is available which can change the course of myotonic dystrophies. But following measures can help to reduce disability, prevent cardiopulmonary complications and also help parents in family planning.

18.7.1 Cardiac Arrhythmias

Both DM 1 and DM 2 patients are at risk of sudden cardiac death due to brady- and tachyarrhythmias. Patients need periodic ECG, 2D Echo and Holter monitoring for detection of rhythm abnormalities. Appropriate intervention in the form of pacemaker implantation and implantable cardioverter defibrillator can help to prevent sudden cardiac death (Dello Russo et al. 2009).

18.7.2 Respiratory Compromise

Altered sleep pattern, excessive daytime sleepiness, central apnoea and respiratory muscle weakness contribute to respiratory distress and can contribute to premature mortality in patients with DM. In few studies, modafinil (200–400 mg) has been found to be effective in reducing daytime sleepiness (MacDonald et al. 2002; Talbot et al. 2003; Wintzen et al. 2007). Judicious use of non-invasive ventilatory support can be helpful (Thornton 2014).

18.7.3 Myotonia

In 2006, Cochrane review documented that to date there was lack of good-quality data and randomised studies on pharmacotherapy of DM. In small studies, clomipramine and imipramine have short-term beneficial effect (Trip et al. 2006). In 2010, mexiletine (150 and 200 mg three times daily) was found to be as effective as an antimyotonic agent in DM 1 (Logigian et al. 2010). In the author's personal experience, membrane stabilisers are of only modest benefit as myotonia is not the limiting issue in DM.

18.7.4 Cataract

It needs conventional surgical treatment, but anaesthetic risk should be taken care of in DM 1 patients (Udd and Krahe 2012).

18.7.5 Exercise

It was found that strength training and aerobic exercises do not have any beneficial effects but are not harmful. However, it can help to prevent disuse-related atrophy (Voet et al. 2010).

18.7.6 Dehydroepiandrosterone

These were not found to be helpful in improving muscle strength in patients with DM (Penisson-Besnier et al. 2008).

18.7.7 Prenatal Genetic Testing

According to international myotonic dystrophy consortium, prenatal genetic testing can be used to assess foetal risk at 10 or 12 weeks if a parent has been diagnosed with DM 1 (The International Myotonic Dystrophy Consortium (IDMC) 2000).

18.8 Prognosis

Congenital DM 1 can be fatal in up to one fourth cases in infancy and those who survive succumb to illness in mid-30s (Thornton 2014; Reardon et al. 1993). DM 1 can lead to severe morbidity and patient becomes disabled by 30–50 years. It can cause premature mortality due to severe cardiorespiratory involvement. Prognosis depends on age at onset of illness and number of repeats (Meola and Cardani 2015; Udd and Krahe 2012). As the abnormalities are less severe in DM 2 than in DM 1 and disease progression is slower, prognosis and life expectancy are more favourable in DM 2. However, the presence of severe cardiac abnormalities can be life threatening in DM 2 (Finsterer 2002).

18.9 Case Study

Clinical details: A 23-year-old male presented with history of difficulty in opening tight fist, of 1-year duration. This tightness reduced with repeated efforts. There was no aggravation of these symptoms on exposure to cold. There was no pain, difficulty in opening eyelids, dyspnoea, bulbar complaints and distal or proximal limb weakness. There was no history of cardiac disease, cataracts, baldness or myotonia in family members. On examination, there was mild temporal hollowing, action and percussion myotonia in thenar muscles and extensor muscles. There was no baldness, ptosis, facial or bulbar weakness. However, patient had hypertrophy of calf muscles, but other muscles were normal (Fig. 18.3). There was no eyelid or tongue myotonia and patient did not have paradoxical worsening of myotonia. Power, sensory examination and deep tendon reflexes were normal.

Summary: A 23-year-old man with myotonic disorder, temporal hollowing and calf hypertrophy without any weakness or extra muscular manifestations.

Discussion: Investigations revealed CK value of 394 IU, normal thyroid and cardiac evaluation. NEE showed myotonic discharges without any myopathic potentials. Possibility of myotonic disorder such as myotonia congenita was likely as patient did not have weakness or features of dystrophy. Although patient did not

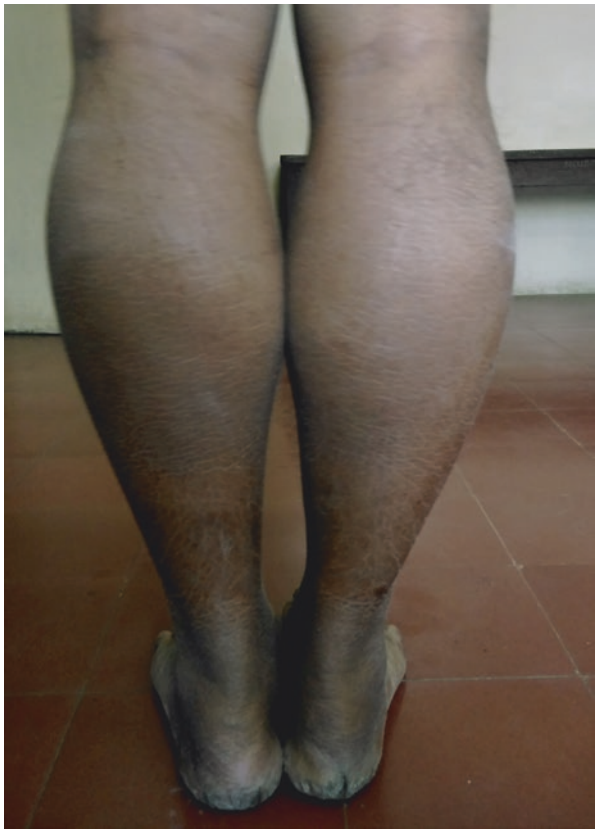

Fig. 18.3 Hypertrophy of calf muscles

have typical myotonic facies, mild temporal hollowing was observed, and hence, possibility of DM was also considered. Genetic testing revealed CTG repeat expansion >150 in DMPK gene and MC gene panel was normal. Thus, diagnosis of DM 1 was confirmed. Calf hypertrophy and absence of muscle weakness have been rarely reported with DM 2. This case exemplifies the overlap of presentations between dystrophic and nondystrophic myotonias.

Key Points

When to suspect

- Combination of weakness and myotonia
- Characteristic facial features
- Extramuscular features: cataract, balding, infertility, diabetes, cardiac arrhythmias
- DM 2: proximal myopathy with myotonia

How to diagnose

- Electrophysiological demonstration of myotonic discharges
- TP-PCR and Southern blotting showing the triplet repeat expansion

How to treat

- Mexiletine, phenytoin, other membrane stabilisers
- Treat cardiac arrhythmia
- Treat hyperglycemia
- Physical therapy

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Distal Myopathies

19

19.1 Introduction

In most primary muscle diseases, proximal muscles are predominantly affected. Some myopathies preferentially affect distal or semi-distal limb muscles from the early stage of the disease (Malicdan and Nonaka 2008). Distal myopathies form a heterogeneous group of genetic disorders which affect lower limb muscles, and uncommonly, the predominant involvement is of the upper limbs. In lower limbs, the brunt of weakness can be on either the anterior or the posterior compartments of the leg. Clinical features may overlap and apparently similar phenotypes can have distinct genetic basis (Mastaglia and Laing 1999). Recent developments in molecular genetics have characterised at least 20 distinct disorders (Udd 2014). Some distal myopathies are well entrenched in the literature and often have clinically recognisable features. In this chapter, we have referred to these as the classical forms of distal myopathies and are tabulated below (Table 19.1):

The group of distal myopathies also includes the myofibrillar myopathies (MFM) which are characterized by distinct pathological pattern associated with accumulation of myofibrillar degradation products. Out of the various clinical patterns, some of these MFM tend to have predominant distal weakness, and such forms are tabulated below (Table 19.2) (Selcen 2011; Dimachkie and Barohn 2014; Palmio and Udd 2016):

Some less common myopathies are also described in the spectrum of distal myopathies. These are mentioned below in Table 19.3:

As the disease duration increases, a large proportion of patients with distal myopathy develop proximal weakness and vice versa. So, at some stage in the illness, a large number of myopathy patients have some degree of distal weakness. Hence, an updated classification and diagnostic approach are required to narrow down differentials and order for specific genetic tests (Udd 2014).

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Table 19.1 Classic distal myopathies

Disease	Protein	Gene
GNE myopathy (DMRV or hiBM 2 or Nonaka myopathy or quadriceps sparing myopathy)	GNE	GNE
Dysferlinopathy (Miyoshi myopathy 1)	Dysferlin	DYSF
Distal anoctaminopathy (Miyoshi myopathy 2)	Anoctamin 5	ANO5
Zaspopathy (Markesbery–Griggs)	ZASP	LDB3
Laing distal myopathy	Beta myosin heavy chain	MYH7
Udd myopathy (distal tibial myopathy or titinopathy)	Titin	TTN
Welander myopathy	TIA1	TIA1

DMRV distal myopathy with rimmed vacuoles, *hIBM2* hereditary inclusion body myopathy type 2, *GNE* UDP-N-acetylglucosamine 2-epimerase, *ZASP* Z-disc alternatively spliced PDZ domain-containing protein, *TIA1* T-cell restricted intracellular antigen

Table 19.2 Classification of myofibrillar myopathies with distal limb weakness

Disease	Protein	Gene
MFM1	Desmin	DESM
MFM2	AlphaB-crystallin	CRYAB
MFM3	Myotilin	TTID
MFM5 (Williams distal myopathy)	Filamin C	FLN C

Table 19.3 Less common distal myopathies

Disease	Protein
Distal myopathy with vocal cord and pharyngeal weakness	Matrin 3
VCP-mutated distal myopathy	VCP
KLHL9-mutated distal myopathy	KLHL9
Distal nebulin myopathy	Nebulin
Telethoninopathy	Telethonin
Oculopharyngodistal myopathy	Still unknown

VCP valosin-containing protein

19.2 Classic Distal Myopathies

19.2.1 Epidemiology

There is significant regional variation in prevalence of distal myopathies. Nonaka and colleagues observed existence of an autosomal recessive distal myopathy in Japan, with the brunt of weakness in tibialis anterior muscles. At the same time, Argov and Yarom described hIBM 2 in Iranian Jews and pointed out the sparing of quadriceps muscles. They called this condition, quadriceps sparing myopathy. Both the groups showed rimmed vacuoles in the muscle biopsies. Later on, it was almost simultaneously detected that Nonaka myopathy, DMRV and hIBM 2 were allelic and caused by mutations in same gene, i.e. GNE. Thus, these conditions are

now known as GNE myopathy (Eisenberg et al. 2001; Nishino et al. 2002 and Kayashima et al. 2002). GNE myopathy is common in Japan and Middle East and is increasingly reported from all over the world (Udd 2014). Small case series of GNE myopathy have been reported from Southeast Asia and India (Liewluck et al. 2006 and Nalini et al. 2013). Miyoshi first reported the first phenotype of dysferlinopathy in 1967. For a time, Miyoshi myopathy was thought to be restricted to Japan but later has been reported from Europe and elsewhere (Urtizberea et al. 2008). Few case reports and series of Miyoshi myopathy based on immunohistochemistry have been reported from India (Khadilkar et al. 2004; Nalini and Gayathri 2008; Shyma et al. 2015 and Pradhan 2006). Anoctaminopathy is one of the recently recognised forms of distal myopathies and is one of the most common myopathies in Europe (Udd 2014; Penttilä et al. 2012a, b and Sarkozy et al. 2013). Udd myopathy is one of the most common muscle diseases in Finland but has rarely been reported from other countries. Markesbery–Griggs variety is another distal myopathy that has been reported mostly from European countries (Udd 2014). Welander observed autosomal dominantly transmitted late-onset distal myopathy in 1951 in Sweden and is the earliest description of distal myopathies. Welander myopathy is common in Sweden and Finland but rarely reported from other countries (Mastaglia et al. 2005 and Udd 2014). Laing myopathy was first reported from Australia but now genetically proven cases have been reported from the United States and Europe (Mastaglia et al. 2005). While most of distal myopathies do not have any sex predilection, male preponderance has been noted in anoctaminopathy (Penttilä et al. 2012a, b and Sarkozy et al. 2013).

19.2.2 Clinical Features

Based on age at onset, inheritance pattern, initial weakness and associated features, classic distal myopathies can be analysed as follows in Table 19.4:

Table 19.4 Clinical analysis of classic distal myopathies

Disease	Age at onset	Inheritance	Initial weakness	Other associated features
GNE myopathy	Usually third decade but can be earlier	Autosomal recessive	Ankle dorsiflexors (foot drop) (Fig. 19.1)	Proximal weakness with sparing of quadriceps; rarely upper limb onset; can be asymmetrical
Dysferlinopathy	Late teens or early adulthood	Autosomal recessive	Calf swelling and pain followed by calf weakness and atrophy (Fig. 19.2); inability to stand tiptoe and hop	Associated proximal weakness of posterior thigh muscles; onset in anterior tibial muscles is known as DMAT

(continued)

Table 19.4 (continued)

Disease	Age at onset	Inheritance	Initial weakness	Other associated features
Distal anoctaminopathy	20–25 years but can occur up to 35 years	Autosomal recessive	Asymmetrical calf atrophy preceded by pain and transient calf swelling	Male preponderance; associated proximal weakness; asymmetry is common
Udd myopathy	>35–40 years	Autosomal dominant	Ankle dorsiflexors (foot drop)	Later on, hamstring weakness; hands are spared
Zaspopathy	>40–50 years	Autosomal dominant	Ankle dorsiflexors (foot drop)	Fingers and wrist extensors; cardiomyopathy
Laing myopathy	Childhood	Autosomal dominant	Ankle and toe extensors (foot drop and hanging big toe)	Wrist and finger extensors weakness; neck flexor and later on axial muscles weakness
Welander myopathy	>50 years	Autosomal dominant	Wrist flexors and small muscles of hands	Later on toe and ankle extensor weakness; mild sensory loss

DMAT distal myopathy with onset in tibialis anterior
Udd (2014), Lamont et al. (2006), Nishino et al. (2015), Urtizberea et al. (2008), Paradas et al. (2010), Pradhan (2008, 2009), Khadilkar et al. (2004, 2008a), Penttilä et al. (2012a, b), and Mastaglia et al. (2005)

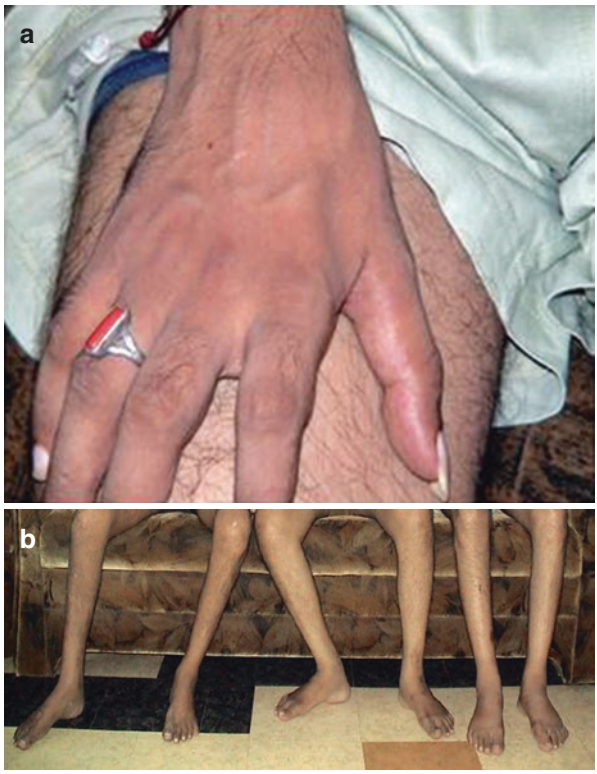

Fig. 19.1 (**a**) Wasted first dorsal interosseous and (**b**) anterior compartment of legs in a family with GNE myopathy

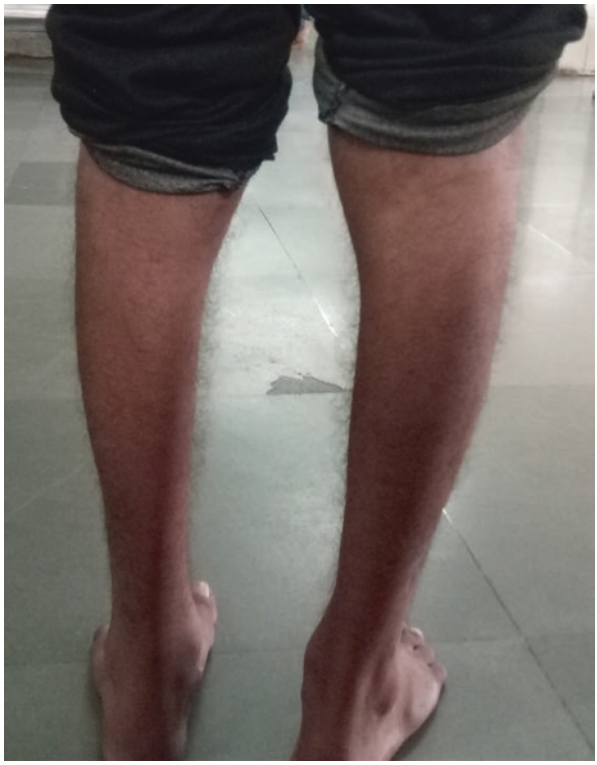

Fig. 19.2 Calf atrophy in a patient with dysferlinopathy

19.2.3 Pathophysiology

Distal myopathies have apparently similar phenotypes but underlying molecular defects are different. Histopathological changes of rimmed vacuoles are commonly found in many of the distal myopathies. Most distal myopathies have been genetically characterized. Genetic mutations and affected proteins are summarised in Table 19.1.

19.2.4 Investigations

Once a diagnosis of distal myopathy is suspected, serum biochemistry, MRI imaging of muscles, muscle biopsy and the genetic evaluation are utilised to arrive at the definitive diagnosis. Recent developments in MRI of muscles have been significant and pattern recognition is increasingly refined. Genetic panels are being evolved to study multiple candidate genes at the same time, reducing the turnover time for diagnosis. Table 19.5 summarises the investigative characteristics.

Table 19.5 Investigations in classic distal myopathies

Diseases	Creatine kinase (CK)	Muscle biopsy	MRI muscles pointing to fibrofatty degeneration and atrophy
GNE myopathy	Modest elevation between two and four times	Rimmed vacuoles; myopathic changes	Tibialis anterior, toe extensors, posterior and medial compartment of the thigh involved; milder involvement of posterior compartment of the leg and rectus femoris; sparing of the vastus medialis (Fig. 19.3)
Dysferlinopathy	Moderate to severe elevation; more than 10 times; can be elevated up to 150 times	Scattered necrosis; inflammatory infiltrates can be seen; absence of vacuolar changes	Posterior compartment of the leg and thighs involved and later on anterior compartment; sparing of the medial head of gastrocnemius, gracilis and sartorius
Distal anoctaminopathy	Similar to dysferlinopathy	Scattered necrosis; myopathic changes; absence of vacuoles	Asymmetrical posterior compartment of the leg and thighs involved; sparing of gracilis, sartorius and anterior compartment of the leg
Udd myopathy	Normal or slightly increased	Rimmed vacuoles and myopathic changes	Anterior compartment of the leg severely involved; affection of hamstrings later on; focal changes in posterior compartment of the leg
Zaspopathy	Normal or slightly increased	Rimmed and non-rimmed vacuoles; myopathic changes; myofibrillar degeneration can be seen	Earliest in medial gastrocnemius; severe affection of anterior compartment of legs later on involves all muscles of legs and thighs
Laing myopathy	Moderately elevated up to eight times of normal	Type 1 fibre atrophy; congenital fibre-type disproportion; absence of vacuoles	Toe and ankle extensors severely affected; all thigh muscles, paraspinals and neck muscles show changes; relative sparing of posterior compartment of the leg, sartorius
Welander myopathy	Normal or slightly increased	Rimmed vacuoles; myopathic changes	Involvement of anterior >> posterior compartment of the leg

O'Ferrall and Sinnreich (2013), Dimachkie and Barohn (2014), Udd (2012), Urtizberea et al. (2008), Wattjes et al. (2010), Kesper et al. (2009), Sarkozy et al. (2012), and Tasca et al. (2012a, b)

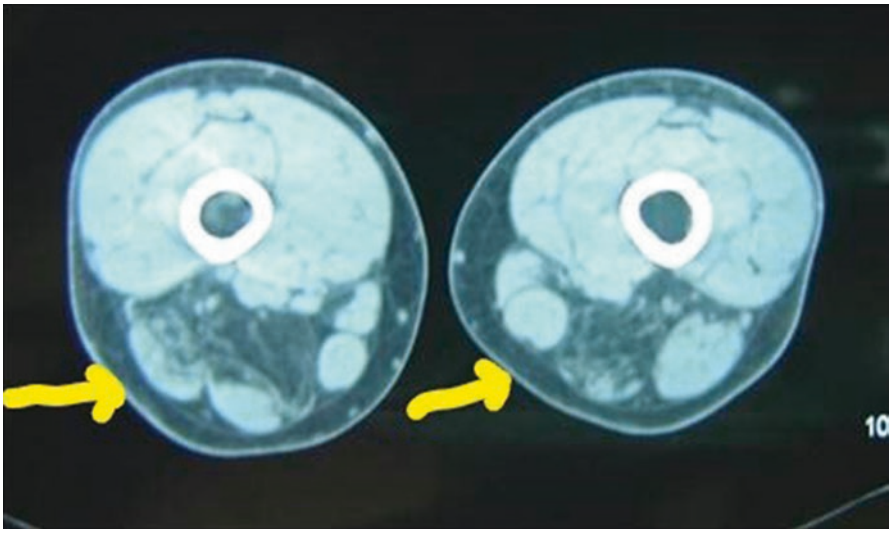

Fig. 19.3 MRI thigh shows wasting and fatty replacement of posterior thigh leg muscles (*arrows*). Quadriceps is well preserved

19.2.5 Differential Diagnosis

As distal myopathies are uncommon, omission errors are well recognised in the diagnostic process. Following conditions closely resemble distal myopathies and need to be differentiated from distal myopathy (Table 19.6).

19.2.6 Management

Definitive therapies for distal myopathies are in experimental phase, and at present, management of distal myopathies remains largely supportive.

19.2.6.1 Definitive Treatment

GNE encodes for enzymes involved in biosynthesis of sialic acid. Mutations in GNE lead to decreased production of sialic acid. Hence, efforts are being made either to supplement sialic acid or to deliver normally functioning gene into affected muscles. Sialic acid extended release (SA-ER), a slow release product developed by Ultragenyx, was administered in doses of 3 or 6 g per day to 46 patients with GNE myopathy. The first phase of trial proved that sialic acid is safe and showed modest improvement in the upper limb functional measurements, and patients with greater walking ability had better effect. Phase 2 of this trial has been completed but results are yet to be declared (Nishino et al. 2015 and https://clinicaltrials.gov/ct2/show/study/NCT01517880). Phase 3 randomised, double-blind, placebo-controlled studies are ongoing to evaluate sialic

Table 19.6 Differential diagnosis of distal myopathies

Diseases	Key distinguishing features
Polymyositis can mimic dysferlinopathy due to presence of pain, progressive weakness, high CK elevation and inflammatory changes on muscle biopsy	Elderly onset, proximal weakness out of proportion to wasting, shoulder girdle and neck weakness, bulbar involvement, no differential weakness, absence of hypertrophy, absence of involvement of family members, raised ESR, active potentials on NEE and inflammatory infiltrates in non-necrotic fibres favour polymyositis. These patients can have fever prior to onset of weakness (Khadilkar et al. 2008a, b)
Hereditary sensory motor neuropathy (HMSN) is probably the closest differential diagnosis	First to second decade onset, symmetrical wasting, foot deformities, absence of differential weakness, thickened nerves, small muscles of hands involved, areflexia, sensory loss, absence of SNAPs, neurogenic potentials on NEE and nearly normal CK levels. Preserved EDB bulk in the presence of severe toe weakness and presence of cardiomyopathy favours distal myopathy
Distal spinal muscular atrophy	Similar to HMSN except for sensory involvement (refer to chapter on SMA)
X-linked spinobulbar muscular atrophy (Kennedy disease)	Bulbar onset, perioral fasciculation, distal > proximal weakness, features of androgen resistance like gynaecomastia and associated sensory neuropathy. Elevated CAG trinucleotide repeat is diagnostic
Lambert–Eaton myasthenic syndrome can present with distal weakness and later on wasting. NEE may show myopathic potentials	Triad of pain, fatigable weakness and autonomic symptoms. Associated mild ptosis, neck and bulbar weakness, more than 100% increment on RNS

NEE needle electrode examination, *SNAP* sensory nerve action potential, *EDB* extensor digitorum brevis, *RNS* repetitive nerve stimulation

acid in GNE myopathy (https://clinicaltrials.gov/ct2/show/NCT02377921). A safety trial of SA-ER in GNE patients with severe ambulatory impairment is underway (https://clinicaltrials.gov/ct2/show/NCT02731690). Liposomal systemic GNE delivery conducted on a single patient showed minimal effect on muscle function but concluded that infusions have to be intermittently repeated (Nemunaitis et al. 2011). In a mouse model, correction of GNE functions and increase in sialic acid correlated with improvement in muscle mass, strength, pathology and body weight, and they provided proof of concept evidence for starting clinical trials in humans (Nishino et al. 2015). A trial is currently recruiting patients for gene therapy in individuals with DYSF gene mutation (https://www.jain-foundation.org/patient-physician-resources/clinical-studies-and-trials/clinical-studies-and-trials-lgmd2bmiyoshi-my).

19.2.6.2 Supportive Therapy

It is important to screen sufferers of distal myopathies, in general, and MFM, in particular, for cardiac involvement. Patients with symptoms of palpitation and syncope and those who have abnormal ECG or 2D Echo should be referred for further

Table 19.7 Prognosis of classic distal myopathies

Diseases	Prognosis
GNE myopathy	Early adulthood onset, severe progression in first few years and patients may lose ambulation after 10–15 years of disease progression
Dysferlinopathy	After 20 years, both proximal and distal muscles are severely involved and cause severe walking difficulty
Distal anoctaminopathy	Disease progression is very slow; distal upper limbs may remain spared. Ambulation is preserved till late
Udd myopathy	Late onset of distal weakness and proximal weakness occurs in sixth to seventh decade. Patients usually remain ambulatory
Zaspopathy	Walking may compromise after 15–20 years of illness as proximal weakness ensues. Due to cardiac involvement, patients may require pacemaker
Laing myopathy	Though onset is early, disease progression is slow. Ambulation may be compromised due to axial muscle weakness, scoliosis, and proximal involvement
Welander myopathy	As disease onset is in fourth to fifth decade and progression is very slow, patients usually remain ambulatory and have a normal life span

Udd (2014) and Penttilä et al. (2012a, b)

cardiac evaluation and intervention. Submaximal strength training and mild aerobic exercises can improve muscle efficiency and cardiac performance and are probably safe. Foot bracing and orthosis help to improve function in patients with distal limb weakness (Narayanaswami et al. 2015 and O'Ferrall and Sinnreich 2013).

19.2.7 Prognosis

Distal myopathies are slowly progressive, mainly lead to restriction in ambulation and are not known to cause premature death. Early onset of illness is more prone to compromise ambulation than late-onset distal myopathies. Prognosis of distal myopathies is summarised below (Table 19.7).

19.3 Myofibrillar Myopathy (MFM)

MFM is a group of disorders that have a characteristic pathological pattern of myofibrillar degeneration beginning at Z-disc and accumulation of myofibrillar degradation products (Selcen 2012). Despite having common pathological features, underlying genetic defects are different (Dimachkie and Barohn 2014). They have diverse clinical features ranging from proximal weakness at onset to initial distal weakness. In some patients, cardiomyopathy can precede muscle weakness. Few MFM that can have predominant distal weakness at onset are described below (Selcen 2010) (Table 19.8).

Table 19.8 Clinical features of distal forms of MFM

Features	MFM1 (Desmin)	MFM2 (alphaB crystallin)	MFM3 (myotilin)	MFM5 (filamin C)
Age at onset	Adults; but can vary from 10 to 61 years	Late adulthood	Late adulthood	Fifth decade
Initial weakness	Distal leg	Distal leg in late cases; proximodistal in early onset	Distal leg	Distal upper limbs and hands; but can have onset in legs
Inheritance	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant
Other features	Prominent cardiomyopathy than can precede muscle weakness; bulbar weakness	Cardiomyopathy, cataract, bulbar weakness	Proximal lower and upper limb weakness, cardiomyopathy, peripheral neuropathy	Cardiac involvement
CK level	Mild to moderate increase	Mild increase	Mild increase	Mild increase
Muscle biopsy	Myofibrillar changes, rimmed vacuoles, desmin deposition	Myopathic changes, desmin deposition	Myofibrillar changes, vacuoles, myotilin deposition	Myopathic changes, vacuolation, desmin aggregates
Muscle MRI	Lateral peroneal > anterior tibial > posterior calf. Semitendinosus involvement is specific	Similar to desmin	Similar to Zaspopathy	Distal upper limbs, posterior calf and proximal lower limb muscles involved; anterior compartment of leg spared
Prognosis	Severe cardiac involvement can be life threatening	Can affect ambulation in late stages	Relatively rapid progression and loss of ambulation within 10 years	Can affect ambulation in late stages

Udd (2014), Dimachkie and Barohn (2014), Olivé et al. (2005), Selcen (2011), and Narayanaswami et al. (2015)

19.4 Other Uncommon Distal Myopathies

Recently, few myopathies with onset in distal limb muscles have been identified and have specific molecular basis. These myopathies have been described in a small number of patients, and their key features have been tabulated in Table 19.9.

Table 19.9 Key features of uncommon distal myopathies

Disease	Protein	Key clinical features
Distal myopathy with vocal cord and pharyngeal weakness	Matrin 3	Distal weakness in ankle, toe extensors or finger extensors at onset, associated with vocal cord and pharyngeal weakness, mild CK elevation. Described in 2 families
VCP-mutated distal myopathy	VCP	Distal leg weakness at onset in late adulthood. Associated with proximal weakness, features of Paget's disease and frontotemporal dementia
KLHL9-mutated distal myopathy	KLHL9	Childhood to early adulthood onset distal leg more than calf weakness
Distal nebulin myopathy	Nebulin	Childhood-onset ankle dorsiflexors and finger extensor weakness. Slow progression. Muscle biopsy may show grouped atrophy
Telethoninopathy	Telethonin	Early onset, anterior tibial weakness, later on proximal weakness, calf hypertrophy, moderate CK elevation and sometimes cardiac involvement
Oculopharyngodistal myopathy (Satoyoshi myopathy)	Still unknown	Distal leg and forearm weakness in 30s and 40s, ophthalmoparesis and bulbar weakness

Mastaglia and Laing (1999), Dimachkie and Barohn (2014), Udd (2014), and Narayanaswami et al. (2015)

19.5 Case 1

Clinical details: A 55-year-old man noticed gradually progressive weakness of both lower limbs since age of 25 years. Initially, he noticed weakness of the left calf and soon within months the right calf weakened. In the ensuing 3 years, he developed bilateral progressive foot drop (Fig. 19.4). Over the next few years, he developed wasting of calves and then anterior leg muscles, which was much more prominent on the left calf. Since 10–11 years, he noticed gradually progressive weakness of both lower limbs and had developed difficulty in getting up from chair. Since 5–6 years, he has noticed mild weakness of arms associated with wasting, more noticeable on the left side. On examination, there was evidence of asymmetric (left > right), bilateral distal > proximal lower limb weakness affecting plantar flexors > dorsiflexors, quadriceps, hamstrings and hip adductors. Deep tendon reflexes were present. Sensory examination was normal. His brother was also affected with similar phenotype. Investigations revealed CK value of 3430 U/L. NEE showed myopathic potentials.

Summary: Familial, slowly progressive, asymmetric distal (calves > anterior leg muscles) > proximal lower limb weakness followed by wasting, mild affection of upper limb proximal muscles and much elevation of serum CK.

Discussion: Since calves were affected at the onset of illness, possibilities of dysferlinopathy and anoctaminopathy were considered. The asymmetry of weakness, very gradual course of the illness and involvement of upper limbs starting after

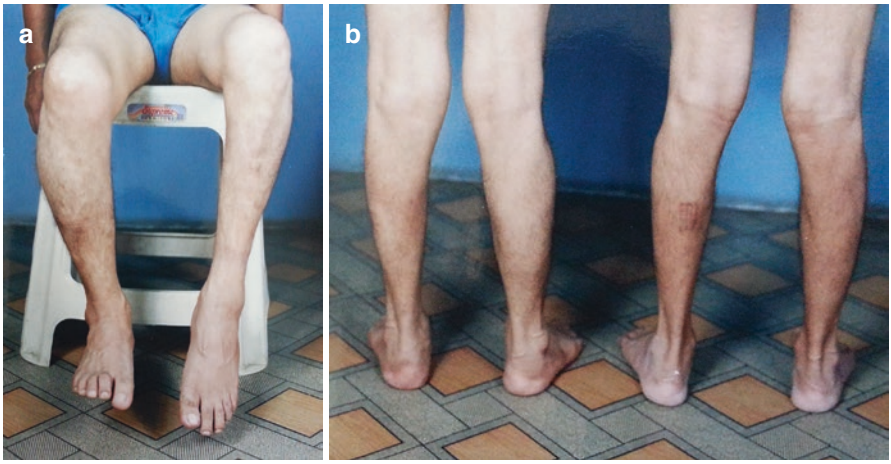

Fig. 19.4 (**a**) Asymmetrical *left* > *right* foot drop and (**b**) asymmetrical calf atrophy (*left* > *right*) in brothers with anoctaminopathy

almost 30 years of illness favoured anoctaminopathy. On genetic testing, no mutation was detected in dysferlin gene. There was homozygous mutation in ANO5 gene which suggested diagnosis of anoctaminopathy.

19.6 Case 2

Clinical details: A 38-year-old man presented with slowly progressive bilateral foot drop over a period of 2 years. He was born of nonconsanguineous marriage and had no family members affected. He had no cardiac complaints. Patient was unable to walk on heels but was able to walk on toes. He also had hamstrings and hip adductor weakness. Power in muscles of upper limbs was normal. All deep tendon reflexes were preserved. Investigations revealed CK value of 521 IU and ECG showed right bundle branch block. On NEE, myopathic potentials were present. MRI of muscles of the leg showed differential involvement with severe affection of anterior leg muscles and sparing of the gastrocnemius and tibialis posterior.

Summary: A 38-year-old man with distal more than proximal lower limb weakness with cardiac rhythm abnormalities and mildly elevated CK levels.

Discussion: As patient had distal-onset muscle weakness involving predominantly anterior compartment of the leg, GNE myopathy, Udd myopathy, Laing myopathy, Zaspopathy and MFM form the list of differential diagnosis. As mentioned in Table 19.8, the presence of cardiac involvement strongly favoured MFM or Zaspopathy. On genetic testing, heterozygous mutation (c.1411T>C) in DES gene was detected. Hence, the final diagnosis was of MFM1.

Key Points

When to suspect

- Distal onset of muscle weakness
- Preference to a set of muscles like ankle dorsiflexors, plantar flexors or thenar muscles (Tables 19.4, 19.8 and 19.9)
- Normal sensations and preserved tendon reflexes
- Cardiac changes

How to investigate

- Elevated CK (marked in some types)
- Electrophysiology excludes neuropathies
- Genetic studies

How to treat

- Supportive therapies

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Distal Hereditary Motor Neuropathy

20

20.1 Introduction

dHMN are a genetically heterogeneous group of rare disorders characterised by distal lower motor neuron weakness. It is also known as distal spinal muscular atrophy (dSMA) or SMA type V. Clinical phenotype of dHMN is similar to Charcot–Marie–Tooth disease (CMT), but sensory system remains unaffected clinically and electrophysiologically in dHMN. Overlap in genotype and phenotype exists between dHMN, CMT2 and familial amyotrophic lateral sclerosis (fALS). dHMN has been classified into its subtypes based on phenotype and underlying genetic defect (Table 20.1). Electrophysiology and genetics are helpful to confirm diagnosis of dHMN in patients with distal lower motor neuron weakness. Presently, management of these rare disorders remains entirely supportive (Harding 1993; Stojkovic 2016; De Jonghe et al. 2002; Rossor et al. 2012 and Rossor 2017).

20.2 Epidemiology

These disorders have been rarely reported and their exact prevalence and incidence worldwide are not known. Except X-linked dHMN, other types of dHMN are known to occur both in males and females.

20.3 Clinical Features

Distal weakness and wasting of limbs, sparing of sensory system and foot deformities are the clinical characteristics of dHMN. Associated clinical features can be helpful to differentiate between various subtypes of dHMN (Table 20.2).

S.V. Khadilkar et al., *Neuromuscular Disorders*,
https://doi.org/10.1007/978-981-10-5361-0_20

Table 20.1 Classification of dHMN

Disease	Genetic defect	Mode of inheritance
dHMN type I	HSPB1, HSPB8, GARS and DYNC1H1	Autosomal dominant
dHMN type II	HSPB1, HSPB8, BSCL2 and HSPB3	Autosomal dominant
dHMN type III	Unknown (locus is 11q13)	Autosomal recessive
dHMN type IV	Unknown (locus is 11q13)	Autosomal recessive
dHMN type V	GARS and BSCL2	Autosomal dominant
dHMN type VI	IGHMBP2	Autosomal recessive
dHMN type VII	DCTN1 and TRPV4	Autosomal dominant
X-linked dHMN	ATP7A	X-linked
dHMN and pyramidal features	SETX and BSCL2	Autosomal dominant
Congenital distal spinal muscular atrophy	TRPV4	Autosomal dominant

ATP7A copper-transporting ATPase 1, *BSCL2* Berardinelli–Seip congenital lipodystrophy type 2, *DCTN1* P150 subunit of dynactin, *DYNC1H1* cytoplasmic dynein heavy chain 1, *GARS* glycyl-tRNA synthetase, *HSPB1* heat-shock protein B1, *HSPB3* heat-shock protein B3, *HSPB8* heat-shock protein B8, *IGHMBP2* immunoglobulin m binding protein 2, *TRPV4* transient receptor vallanoid 4 gene
Irobi et al. (2006), Rossor et al. (2012), and http://neuromuscular.wustl.edu/synmot.html

Table 20.2 Clinical features of various subtypes of dHMN

Disease	Clinical features
dHMN type I	Juvenile-onset distal weakness and wasting in lower > upper limbs; mild subclinical sensory involvement; brisk deep tendon reflexes (DTRs) and mild cerebellar signs can be seen in a proportion of patients
dHMN type II	Similar to dHMN1 but onset is in adulthood
dHMN type III	Slower progression than dHMN I and II
dHMN type IV	Infantile onset; course is similar to dHMN III but the presence of diaphragmatic weakness helps to differentiate between types III and IV
dHMN type V	Onset in second decade of life; upper limb onset in majority of patients
dHMN type VI	Onset in infancy; severe length-dependent weakness; distal predominant; diaphragmatic weakness; poor prognosis
dHMN type VII	Onset in early adulthood; face and arm weakness at the onset followed by leg weakness; vocal cord palsy helps to differentiate dHMN type VII from other forms
X-linked dHMN	Males; length-dependent axonal motor neuropathy presenting as distal weakness and wasting
dHMN and pyramidal features	Distal weakness and wasting associated with pyramidal signs such as brisk reflexes
Congenital distal spinal muscular atrophy	Distal weakness and wasting at birth; arthrogryposis; few patients have associated vocal cord palsy, sensorineural hearing loss; tongue fasciculations

Rossor et al. (2012), Rossor (2017), and http://neuromuscular.wustl.edu/synmot.html

Table 20.3 Genetic defects and affected function in dHMN

Genetic defect	Affected function
GARS	Protein biosynthesis
HSPB1, HSPB3 and HSPB8	Protein modification, folding and degradation
DCTN1and DYNC1H1	Intracellular transport
BSCL2	Endoplasmic reticulum membrane shaping
TRPV4 and ATP7A	Cation channel activity

Weis et al. (2017), Lupo et al. (2016), and Rossor et al. (2012)

20.4 Pathophysiology

Various genetic defects are known to cause dHMN (Table 20.3). dHMN is presumed to be caused by degeneration of anterior horn cells. Different processes in neural function can be affected by various genetic defects leading to dHMN as mentioned in Table 20.3. Diseases caused by dysfunction of chaperones (HSPB) lead to accumulation of misfolded proteins and are called chaperonopathies. Histopathological nerve fibre alterations in hereditary motor neuropathies (HMNs) are largely unexplored due to the limited availability of appropriate tissue specimens.

20.5 Investigations

The clinical phenotype of distal wasting and weakness is caused by many diseases. Hence, investigations are directed towards confirmation of dHMN and ruling out close differential diagnosis. Electrophysiology confirms reduction in motor amplitudes with normal sensory potentials. Needle electrode examination (NEE) shows neurogenic potentials in affected muscles. Preservation of sensory system and presence of neurogenic potentials help to differentiate dHMN from CMT and distal myopathy, respectively. Depending on the phenotype, appropriate genetic tests should be ordered. As this entity is expanding, many patients can have mutations in undiscovered genes (Rossor et al. 2012).

20.6 Differential Diagnosis

It is difficult to differentiate dHMN from other diseases presenting as distal weakness and wasting. Clinical and investigative findings can help in this process (Table 20.4).

Table 20.4 Differential diagnosis of dHMN with their key distinguishing features

Differential diagnosis	Key distinguishing features
CMT—first to second decade onset of distal wasting, weakness and foot deformities	Presence of sensory impairment; depressed deep tendon reflexes; absence of vocal cord and respiratory weakness and absent sensory potentials on electrophysiology favour CMT
Distal myopathy	Preserved EDB bulk in presence of severe toe weakness; involvement of forearm flexors more than intrinsic muscles of hands; elevated creatine kinase (CK) levels; myopathic potentials on NEE and presence of cardiomyopathy favour distal myopathy
X-linked Spinobulbar muscular atrophy [Kennedy disease]	Bulbar onset, perioral fasciculation, distal > proximal weakness, features of androgen resistance like gynaecomastia; associated sensory neuropathy and elevated CAG trinucleotide repeats favour Kennedy disease
Lambert–Eaton myasthenic syndrome (LEMS) can present with distal weakness and wasting	Triad of pain, fatigable weakness and autonomic symptoms are diagnostic. Associated mild ptosis, neck and bulbar weakness, more than 100% increment on RNS and myopathic potentials on NEE point towards LEMS

20.7 Management

Presently, no specific treatment for dHMN is available and management of dHMN remains entirely supportive. Disability due to distal muscle weakness and foot drop can be mitigated by orthosis and rehabilitation.

20.8 Prognosis

The course of all subtypes of dHMN is relentlessly progressive. Few subtypes of dHMN such as type IV and VI are associated with respiratory weakness. Type II has slower rate of progression as compared to other types of dHMN.

20.9 Case

Clinical details: A 32-year-old male developed progressive hoarseness of voice at the age of 15 years. After 2–3 years, he developed right little and ring finger drop due to extensor muscles weakness. Symptoms progressed to involve proximal upper limb muscles on both sides. Weakness was associated with wasting and twitching of muscles. Two years before presentation, he developed difficulty in breathing, and loud breathing sounds were heard when he slept. He also developed severe neck weakness and neck tended to drop while sitting. He had no difficulty in chewing or swallowing but he had to hold his chin up to facilitate swallowing. He had to undergo vocal cord surgery twice in an attempt to improve voice. He had no complaints in lower limbs. On examination, neck flexors, neck extensors and proximal upper limb muscles were wasted and there was scapular winging. Fasciculations were evident

over neck, periscapular region and arms. Patient also had neck drop, right little and ring finger drop (Fig. 20.1), atrophy of thenar muscles and vocal cord paralysis. Sensory examination was normal and all deep tendon reflexes were absent. Family history was not contributory.

Summary: A 32-year-old male having asymmetrical, distal and proximal upper limb weakness, wasting and fasciculations with neck muscles weakness and hoarseness of voice (secondary to vocal cord palsy).

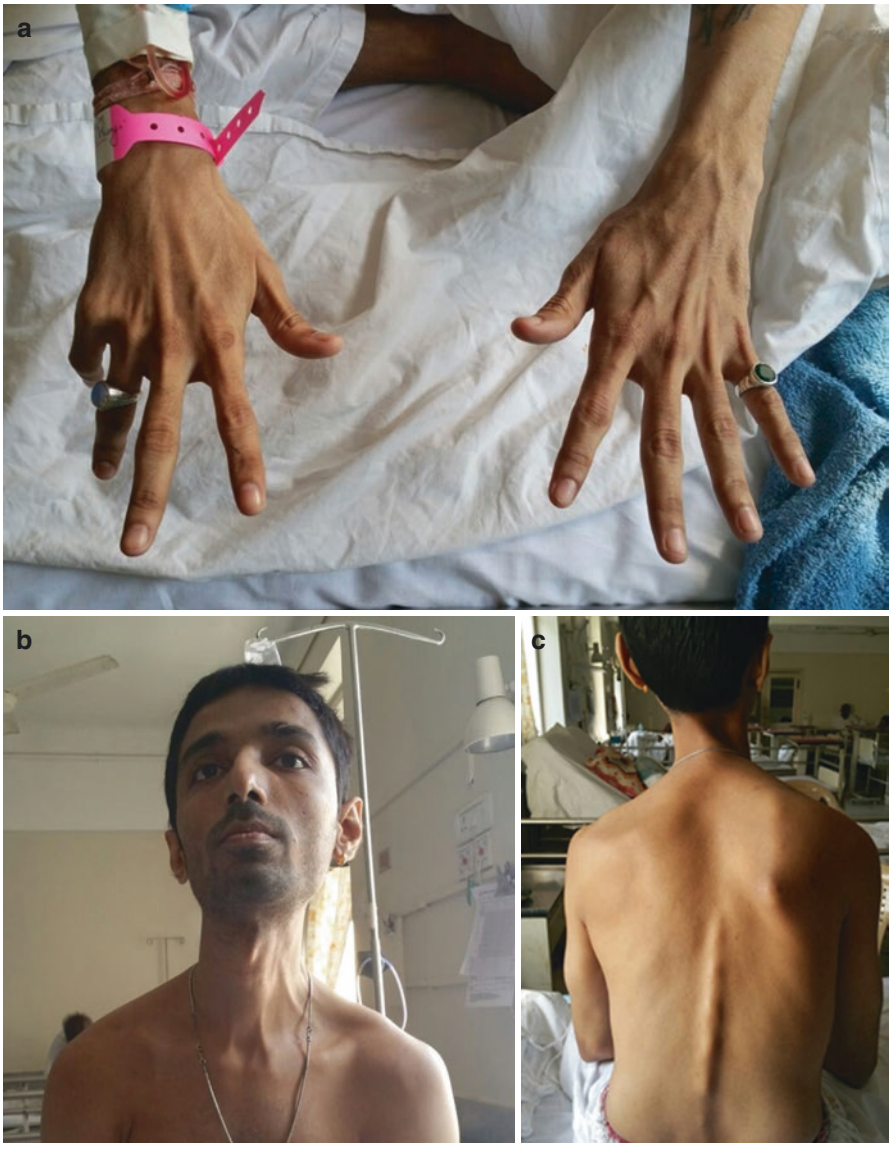

Fig. 20.1 (**a**) Finger drop on the *right side*, (**b**) neck muscle wasting and (**c**) atrophy of periscapular and paravertebral muscles

Discussion: This patient had asymmetrical, proximal and distal weakness, atrophy and fasciculations indicating anterior horn cell as a likely localisation. Electrophysiology demonstrated very chronic, motor axonal denervation in cervical, thoracic and lumbosacral segments. Creatine kinase (CK) levels were normal. In view of pure motor axonal denervation, anterior horn cell (SMA) or motor axon (dHMN) pathology was considered. The vocal cord paralysis and limb weakness pointed to dHMN type VII. Genetic testing confirmed the diagnosis.

It is important to look for associated features (vocal cord palsy in this case) in a patient with suspected anterior horn cell or motor axonal pathology, as it can help to narrow down differentials and facilitate targeted genetic testing.

Key Points

When to suspect

- Distal pure motor weakness
- Foot deformities
- Normal sensations
- Associated features (Table 20.2)

How to diagnose

- Electrophysiology: reduced motor amplitudes with preserved sensory studies
- Genetic evaluation

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Brown–Vialetto–Van Laere [BVVL] Syndrome

21

21.1 Introduction

BVVL syndrome is a rare genetic disease, characterised by progressive pontobulbar palsy, sensorineural hearing loss and spinal anterior horn cell involvement. It was first described by Brown (1894) and later by Vialetto (1936) and Van Laere (1966), respectively.

21.2 Epidemiology

BVVL is uncommon and only over a hundred cases are reported to date. Almost half of these cases are sporadic (Mégarbané et al. 2000), and familial cases are transmitted as autosomal recessive trait. Age of presentation varies from early infancy to adulthood and females outnumber males.

21.3 Clinical Features

In vast majority of cases, first symptom is sensorineural hearing loss which is severe and progressive and is followed by bulbar weakness. In very rare instances, hearing loss may not be present, presumably because such patients die before hearing loss develops. Other initial symptoms are lower motor neuron type of limb weakness and wasting, facial weakness, respiratory insufficiency and shoulder/neck weakness. In BVVL lower cranial nerves (VII to XII) are most frequently affected, but other cranial nerve deficits (II to VI) have also been recorded. Recently, peripheral sensory system involvement (neuropathy or neuronopathy) leading to sensory ataxia has been described (Foley et al. 2014). Other rare symptoms described are mental retardation, seizure, behavioural changes, tremors and autonomic dysfunction. In Fazio–Londe syndrome (FL), the clinical features are similar to BVVL but without the hearing loss. FL is considered to be the same disease as BVVL (Dipti et al. 2005).

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21.4 Pathophysiology

Little is known regarding pathogenesis of BVVL syndrome except the genetic defect. BVVL syndrome is caused by mutations in the SLC52A3 and SLC52A2 gene, encoding the riboflavin transporter hRFT2 and hRFT3, respectively. hRFT3 is highly expressed in human brain and salivary glands, whereas hRFT2 is strongly expressed in the small intestine. These findings suggested a role of hRFT3 in brain riboflavin homeostasis (Yao et al. 2010). Riboflavin is essential for synthesis of flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN). These flavins form a part of various redox enzymes, which are involved in signal transduction, apoptosis and DNA repair. So it is possible that SLC52A2, coding for the riboflavin transporter in the nervous system, plays an important role in neuronal maintenance and homeostasis. Thus, mutations may affect the energy pathway in motor neurons, thereby causing BVVL syndrome (Timmerman and De Jonghe 2014). Bosch et al. (2011) demonstrated the same homozygous mutation in two siblings who presented with BVVL and FL syndromes, respectively, suggesting a common genetic basis for these two diseases.

21.5 Investigations

Imaging of the brain shows no abnormalities in most patients, but transient hyperintense signals in the tegmentum, vestibular nuclei and cerebellar peduncles (Koy et al. 2012), floor of the fourth ventricle and Ponto medullary junction (Koul et al. 2006), bilateral middle cerebellar peduncles (Bandettini Di Poggio et al. 2014), corticospinal tract (Ciccolella et al. 2012) and posterior column (Spagnoli et al. 2014) have been infrequently reported. Neurophysiological studies show low compound muscle action potentials and sensory nerve action potentials depending upon extent and severity of symptoms. Electromyography shows active and chronic denervation in involved segments. Audiometry shows sensorineural hearing loss, and brainstem evoked potentials are abnormal in most of the cases. Visual evoked potentials show abnormalities in clinically affected optic nerves. CSF study shows normal or modest elevation of proteins. Genetic study for mutations in the SLC52A3 and SLC52A2 gene confirms the diagnosis.

21.6 Differential Diagnosis

Bulbar weakness and upper limb wasting occur in a handful of disorders which can have overlapping features. Hence, it is important to differentiate between these diseases (Table 21.1).

21.7 Management

Oral riboflavin supplementation is highly effective in dose of 10 mg/kg/day. Majority of patients stabilise over a period of time and show impressive clinical improvements.

Table 21.1 Differential diagnosis of BVVL with their key differentiating features

Disease	Key differentiating features
Fazio–Londe syndrome	Clinical symptoms are the same except absence of sensorineural hearing loss in Fazio–Londe syndrome
Amyotrophic lateral sclerosis	Adult onset, prominent upper motor neuron signs and rapid progression; mean survival time is less than 3 years, no hearing loss
Nathalie syndrome	Deafness in conjunction with spinal muscular atrophy, cataract, cardiac conduction defects and hypogonadism
Boltshauser syndrome	Distal muscular atrophy with vocal cord paralysis and sensorineural hearing loss. Unlike BVVL, the brainstem signs are restricted to vocal cord paralysis, and the inheritance is likely to be autosomal dominant
Madras motor neuron disease (MMND)	Wasting and weakness of limb muscles, sensorineural deafness and multiple cranial nerve palsies usually affecting cranial nerves VII, IX and XII. Only about 15% of cases of MMND are familial, compared to 50% of BVVL
X-linked spinobulbar muscular atrophy	Adult onset, bulbar onset, perioral fasciculations, features of androgen resistance like gynaecomastia, associated sensory neuropathy, tremors and high 10-year survival rates. CK levels are elevated. Elevated CAG trinucleotide repeats are diagnostic

21.8 Prognosis

Untreated, BVVL syndrome is often fatal. In majority of patients, riboflavin is highly effective and lifesaving. Clinical improvement tends to be rapid but in some patients can be gradual over a period of a year or more. So if the suspicion is high, oral riboflavin should be started as soon as possible without awaiting molecular confirmation.

21.9 Case Study

Clinical details: A 23-year-old male presented with history of bilateral gradually progressive symmetrical ptosis without any diplopia or fluctuations, which began 8 years before presentation. He also developed gradually progressive bulbar weakness, hearing loss and later on weakness and wasting of distal upper limb muscles. Examination confirmed bilateral ptosis without ophthalmoparesis, tongue wasting and fasciculations, sensorineural hearing loss (SNHL) and distal upper limb weakness and wasting (Fig. 21.1). All deep tendon reflexes were elicited on reinforcement. Investigations revealed normal creatine kinase values, and MRI study of the brain and spinal cord was normal. Needle electrode examination showed spontaneous activity and neurogenic potentials.

Discussion: SNHL is an important clinical marker as only a handful of neurological disorders lead to SNHL, e.g. mitochondrial disorders, Fabry's disease, Refsum's disease, neurosarcoidosis and childhood onset of motor neuron diseases. In presence of younger age at onset, tongue fasciculations and wasting with weakness of distal upper limb muscles, a possibility of motor neuron diseases was high in this case. However, ptosis is hardly ever seen in ALS syndromes. Mutation

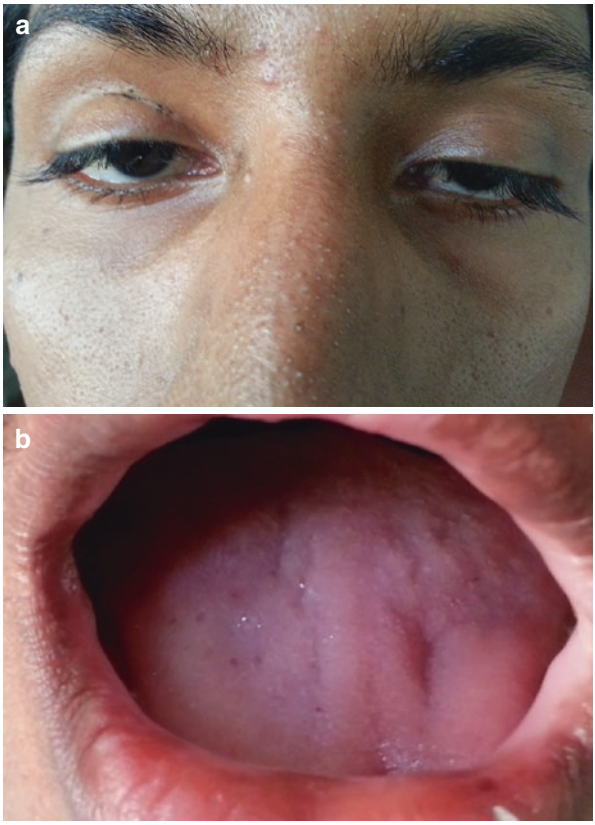

Fig. 21.1 (**a**) Bilateral ptosis and (**b**) tongue wasting

studies for BVVL were not locally available at that time, and with the clinical possibility of BVVL syndrome, he was given riboflavin 200 mg per day. Over a period of 3 months, there was a very impressive improvement in speech and distal upper limb weakness and his quality of life improved much. Recently, the mutation studies for BVVL gene have confirmed abnormalities in this patient. BVVL should be considered in differential diagnosis of childhood-onset tongue wasting and fasciculations, SNHL and distal upper limb weakness, as it is reversible with riboflavin.

Key Points

When to suspect

- Young patient
- Bulbar palsy
- Deafness
- Limb amyotrophy
- Sensory signs in some patients

How to investigate

- Electrophysiology showing fibrillations and chronic de- and reinnervation
- Mutations in the SLC52A3 and SLC52A2 gene

How to treat

- Riboflavin 10 mg/kg/day for prolonged periods

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Part IV

Fluctuating Weakness

Myasthenia Gravis

22

22.1 Introduction

Myasthenia gravis (MG) is an autoimmune disorder affecting the neuromuscular junction of skeletal muscles. The cardinal clinical presentation is fluctuating and fatigable weakness, preferentially affecting ocular, bulbar and proximal group of muscles (Melzer et al. 2016). The weakness in MG can vary from mild ocular symptoms to life-threatening myasthenic crisis. Myasthenic patients experience fluctuations in disease activity and have periods of worsening, exacerbation, improvement and remission (Khadilkar et al. 2014). Ice-pack test, neostigmine test, acetylcholine receptor (AchR) antibody levels, repetitive nerve stimulation and single fibre electromyography (SFEMG) are used for diagnosis of MG (Patil et al. 2016a, b; Larner 2004a, b and Oger and Frykman 2015). Based on clinical manifestations and the presence or absence of specific autoantibodies, MG can be classified into the following subgroups: early-onset MG with AchR antibodies, late-onset MG with AchR antibodies, thymoma-associated MG, muscle-specific kinase (MuSK) MG, lipoprotein receptor-related protein 4 (LRP4) MG, seronegative MG and ocular MG. These subgroups differ in terms of management and prognosis. Hence, it is important to recognise features such as age of onset, pattern of muscle weakness and thymus pathology, as tests to detect all types of antibody levels may not be easily available to all clinicians in a given scenario. Management includes symptomatic and immunosuppressive drugs, avoiding factors that are known to exacerbate illness, supportive therapy during crisis and sometimes thymectomy (Binks et al. 2016; Jayam Trouth et al. 2012; Gilhus and Verschuuren 2015 and Gilhus et al. 2016). Novel biological agents directed against specific molecular targets are in experimental phase and have future potential to be utilised as therapies (Dalakas 2015).

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22.2 Epidemiology

The first case of MG has been reported way back in the seventeenth century. In 1895, at the Berlin society meeting, Jolly described two cases and initially named the condition as 'myasthenia gravis pseudoparalytica'. Later on, MG got accepted as a formal name of this disorder (Jolly 1895). Mary Walker demonstrated improvement in MG symptoms with pyridostigmine as she observed that MG symptoms were similar to that of curare poisoning in 1934 (Walker 1935). In 1959–1960, autoimmune mechanism was proposed by Nastuk and Simpson independently (Nastuk et al. 1959 and Simpson 1960). A decade later, importance of antibodies against AchR was realised in pathogenesis of MG (Patrick and Lindstrom 1973). Historical details of MG have been well documented in some articles (Pascuzzi 1994; Hughes 2005 and Jayam Trouth et al. 2012). In an epidemiological review, prevalence rate of all cases of MG ranged from 15 to 179, AchR MG from 70.6 to 163.5 and MuSK MG 1.9 to 2.9 cases per million populations (Carr et al. 2010). It is generally believed that, AchR MG accounts for 70%, MuSK for 1–10% and seronegative MG forms 10–15% of all cases of MG (Gilhus et al. 2016). MG occurs in both sexes, at all ages, in all races and has been widely reported around the world (Carr et al. 2010). Early-onset and MuSK MG occurs more frequently in females than in males, while late-onset MG is more common in males (Gilhus and Verschuuren 2015 and Gilhus et al. 2016). Large case series of MG have been reported from India, describing clinical presentation, management and long-term prognosis of MG (Singhal et al. 2008; Murthy 2009; Kalita et al. 2014; Khadilkar et al. 2014; Kumar et al. 2016; Murthy et al. 2005 and Sharma et al. 2013). The bimodal presentation, early onset in females and late onset in males, has been documented in all the above-mentioned studies.

22.3 Clinical Features

Fluctuating and fatigable weakness of ocular, bulbar and proximal group of muscles is the clinical hallmark of MG. Severity of weakness varies from 1 day to another and also fluctuates within a day but is generally worse in the evening hours. Weakness is least after rest and sleep while elevated body temperature and sustained exercise increase the degree of weakness. Ocular weakness is most common initial clinical presentation, while oropharyngeal and limb weakness at the onset or in isolation is uncommon (Juel and Massey 2007). In severe cases, weakness progresses to involve neck, trunk and respiratory muscles and patients develop neck drop and severe breathing difficulty requiring mechanical ventilation. Proximal limb muscles are predominantly affected and isolated cases of distal limb weakness have been reported (Fitzgerald and Shafritz 2014). In MuSK MG, isolated ocular involvement is uncommon and is often accompanied by prominent facial and bulbar weakness. Tongue and facial weakness can be severe and patients can develop facial and tongue atrophy (Nikolić et al. 2015 and Guptill et al. 2011). Onset of weakness is acute or subacute, and periods of worsening, exacerbation, improvement and remissions can occur (Vincent et al. 2001 and Khadilkar et al. 2014). Deep tendon reflexes are normal and sensory system remains unaffected in all patients. Clinical features affecting specific group of muscles are tabulated below in Table 22.1.

Table 22.1 Key symptoms and signs in MG

Affected group of muscles	Key symptoms and signs
Ocular weakness is characterised by ptosis, ophthalmoparesis and orbicularis oculi weakness with sparing of pupillary light reflex	Ptosis: Asymmetrical or alternating ptosis is characteristic of MG; over-contraction of frontalis muscles to compensate for ptosis (worried look); worsening of ptosis on sustained upgaze; after prolonged downgaze, upgaze produces excessive lid elevation or Cogan's lid twitch; passively lifting more ptotic eyelid can cause opposite eyelid to fall (enhanced ptosis); improvement in ptosis by application of ice pack for 2 min (Figs. 22.1, 22.2 and 22.3) Ophthalmoparesis: binocular horizontal or vertical diplopia; asymmetrical weakness of multiple extraocular muscles that cannot be attributed to cranial neuropathy; limited adduction in one eye and nystagmoid jerks in opposite eye (pseudo-internuclear ophthalmoplegia); nystagmoid jerks can be seen without any apparent weakness while producing saccades (quiver) Orbicularis oculi weakness: sustained eye closure brings out fatigue of orbicularis oculi and results in involuntary opening of eyes (peek sign). Figure 22.4 demonstrates eye closure weakness in a patient with MG Pupillary light reflex remains normal in all cases Ocular MG: If isolated ocular muscle weakness remains for more than 2 years; then in 90% of patients, illness remains localised to ocular group of muscles. Hence, a minimum of 2-year period of isolated ocular muscle weakness is required for diagnosis of ocular MG
Oropharyngeal weakness	Jaw muscle weakness: chewing difficulty becomes pronounced with prolonged chewing and while chewing hard food; at rest, jaw muscle weakness leads to jaw drop, and patients use their fingers under the jaw to keep the mouth shut; only few diseases can lead to jaw muscle weakness and MG is one of them Facial muscle weakness: expressionless face due to facial muscle weakness; attempts to smile produce upward contraction of medial portions of lip, but outer corners of mouth fail to move (myasthenic snarl) Pharyngeal weakness: nasal twang; nasal regurgitation; difficulty in swallowing solid and liquid foods; risk of aspiration
Axial muscle weakness	Neck flexors and extensor weakness cause neck drop in severe cases; patients may need to support neck with help of hands, i.e. 'dropped head syndrome'; weakness of respiratory muscles leads to respiratory insufficiency and respiratory failure, i.e. 'myasthenic crisis'; it can occur spontaneously or is precipitated by infections, surgery or medications
Limb muscle weakness	MG commonly produces proximal limb muscle weakness; bilateral, symmetrical, weakness restricted to proximal upper limb, e.g. man in the barrel syndrome has been described in MG; less commonly, there can be distal onset in limb muscles

(https://www.uptodate.com/contents/clinical-manifestations-of-myasthenia-gravis, Juel and Massey 2007, Fitzgerald and Shafritz 2014, Vaphiades et al. 2012, Vincent et al. 2001, Gilhus et al. 2016, Shah and Wadia 2016, Werner et al. 2003)

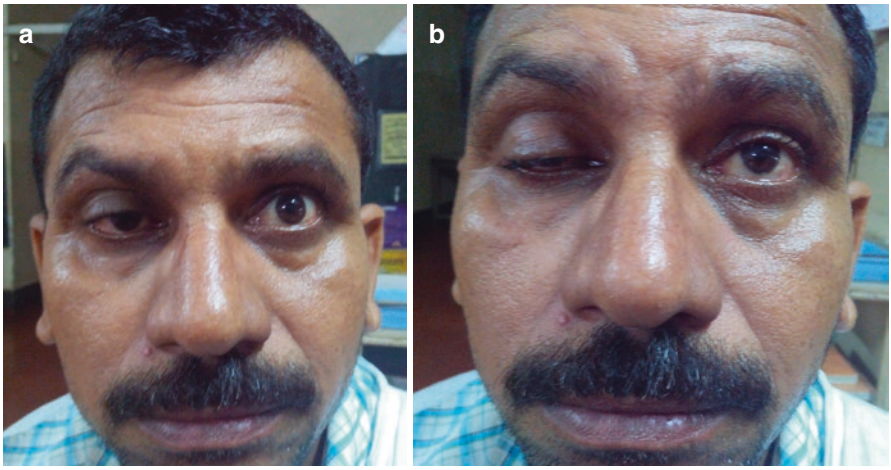

Fig. 22.1 Fatigable ptosis—(**a**) Left eyelid ptosis at rest and (**b**) worsening of ptosis after sustained upgaze for 60 s demonstrating fatigability in a patient with MG

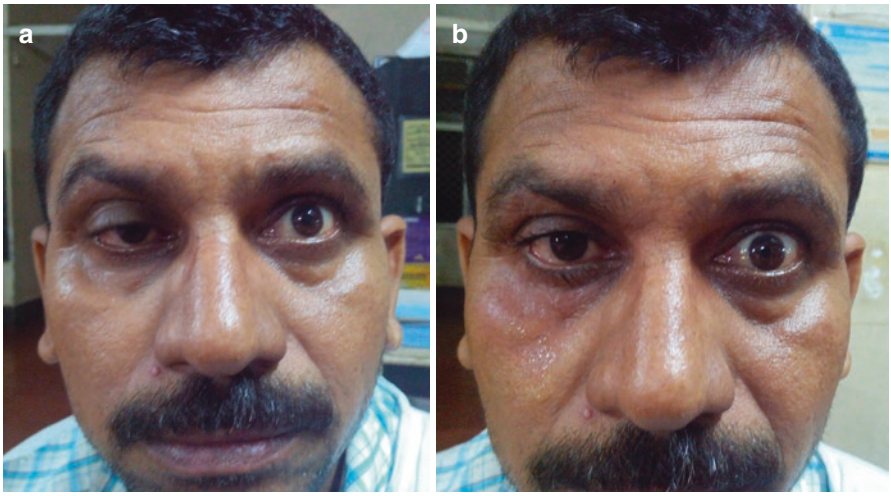

Fig. 22.2 Ice-pack test—(**a**) Left eyelid ptosis at rest and (**b**) improvement of ptosis with application of ice pack in a patient with MG

For quantitative estimation of MG weakness and assessing change in clinical status, a validated quantitative MG (QMG) score is available. It is simple to use, objective and can be performed by the bedside (Barnett et al. 2012 and Bedlack et al. 2005). Following clinical parameters have been included in QMG score:

- Double vision on lateral gaze for 60 s
- Ptosis on upgaze holding for 60 s
- Eyelid closure

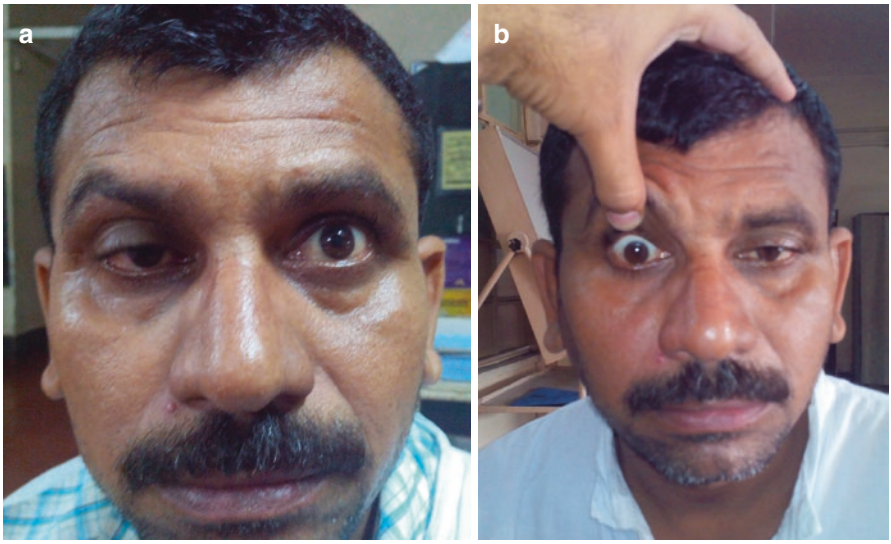

Fig. 22.3 (**a**) Left eyelid ptosis at rest and (**b**) passive lifting of ptotic eyelid cause apparently normal eyelid to fall (enhanced ptosis) in a patient with MG

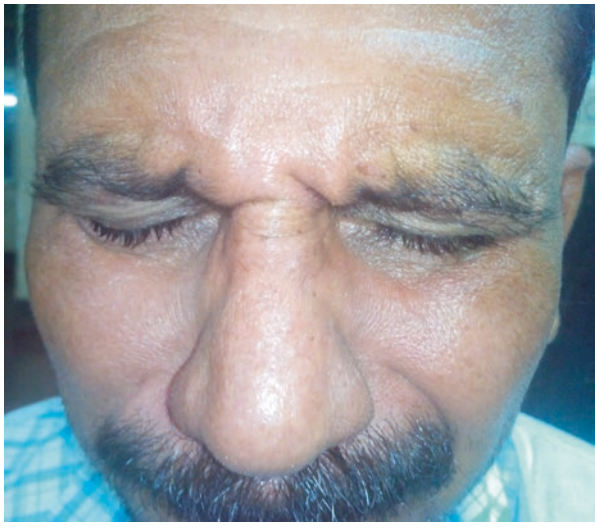

Fig. 22.4 Weakness of orbicularis oculi as demonstrated by incomplete burial of eyelashes in a patient with MG

- Swallowing ½ cup of water
- Speech after counting aloud from 1 to 50
- Both arms outstretched at 90 degrees for 240 s
- Forced vital capacity
- Bilateral hand grip for 45 s
- Head lifted at 45 degrees for 120 s
- Both legs outstretched at 45–50 degrees in supine position for 100 s

Antibodies against proteins in postsynaptic membrane help to define the MG subtype. These subtypes differ in terms of clinical characteristics, associated thymic pathology and response to therapies. Hence, it is important to recognise subtypes of MG. Characteristics of various subgroups of MG are summarised in Table 22.2.

Table 22.2 Key features of various subgroups of MG

Subgroups	Proportion of patients	Key features
Early-onset MG (AchR antibody positive)	15–25%	Age at onset less than 50 years. More common in females than males. Thymic pathology is common, and this group is likely to respond favourably to thymectomy
Late-onset MG (AchR antibody positive)	35–45%	Age at onset more than 50 years. Thymic pathology is rare and this group does not respond well to thymectomy. More common in males than females. Antibodies against ryanodine receptor (RyR) and titin are also present in some patients in whom the disease tends to be severe.
Thymoma MG (AchR antibody positive)	10%	Can occur at any age but peak age at onset is 50 years. Occurs equally in either sex. Symptoms are severe, and there is frequent involvement of neck, bulbar and respiratory muscles. Associations are noted with neuromyotonia and pure red cell aplasia. 70% have anti-RyR and 30% have anti-titin antibodies
MuSK MG (anti-MuSK antibodies positive and anti-AchR antibodies negative)	1–10%	Fourth to fifth decade onset, female preponderance, prominent facial and bulbar involvement, tongue and facial atrophy in severe cases. Less frequent isolated involvement of ocular muscles. Onset is acute and progression is rapid. Poor response or intolerance to acetylcholinesterase inhibitors (ACE-I). The response to plasmapheresis tends to be rapid and dramatic
LRP4 mg	1–5%	In small proportion of MG patients without AchR and MuSK antibodies, anti-LRP4 antibodies can be present. Disease is mild and frequently restricted to ocular muscles, and generalisation is uncommon
Seronegative MG (anti-AchR, anti-MuSK and anti-LRP4 antibodies negative)	10–15% of generalised MG	These antibodies are absent, but in some patients, low affinity or low concentration of antibodies can be detected by using special laboratory testing. In this group, some may have antibodies to RyR or titin. Some patients have antibodies against agrin, Kv1.4 or contactin
Ocular MG	15%	At 2 years after onset, small proportion has weakness restricted to ocular muscles and MG will persist as focal weakness in majority of patients. It can occur in both young and elderly population. Anti-AchR and anti-LRP4 antibodies can be associated with ocular MG. MuSK MG is never associated with isolated ocular weakness. It has not been associated with thymoma, and thymectomy has no role in management of ocular MG

(Guptill et al. 2011; Gilhus and Verschuuren 2015; Gilhus et al. 2016 and Romi 2011)

22.4 Pathophysiology

22.4.1 Neuromuscular (NM) Junction in MG

In normal individuals, action potential at the presynaptic nerve terminals causes release of calcium which facilitates release of acetylcholine and agrin into the synaptic cleft (Fig. 22.5). Binding of acetylcholine to AchR promotes sodium channel opening and, thus, muscle contraction. Agrin binds to MuSK and LRP4, which are required for AchR clustering. In MG, most of the pathogenic antibodies are directed against alpha-subunit of AchR. The mechanisms by which these antibodies inhibit neuromuscular transmission (Fig. 22.6) are:

(a) Block the AchR-binding sites and thus inhibit opening of the sodium channel.
(b) Antigenic modulation that results in internalisation and degradation of surface AchRs.
(c) Complement activation and formation of membrane attack complexes cause destruction of typical folds in the sarcolemma, thus reducing the density of AchRs.

Anti-MuSK and anti-LRP4 antibodies block the intermolecular interactions of MuSK and LRP4, thus disrupting the normal organisation of neuromuscular junction (Fig. 22.6).

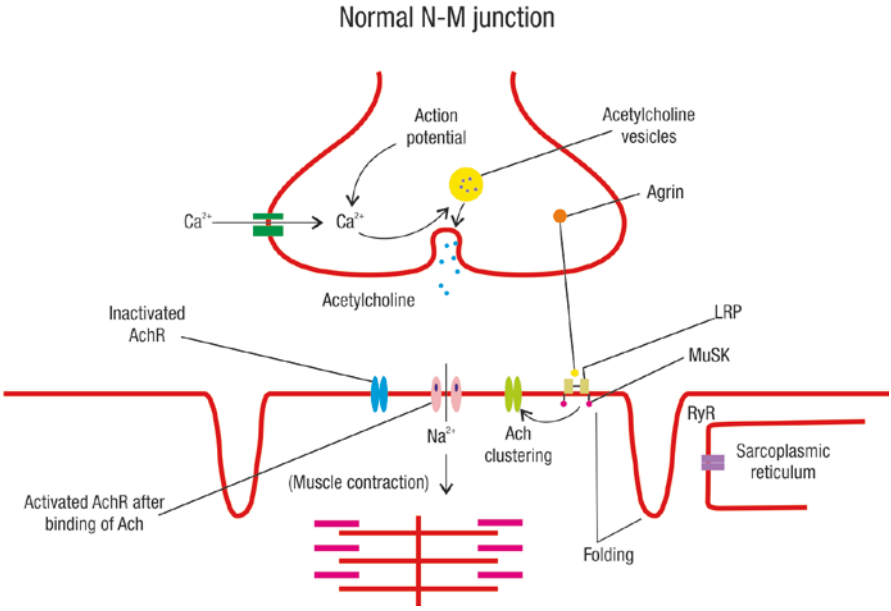

Fig. 22.5 Normal NM junction

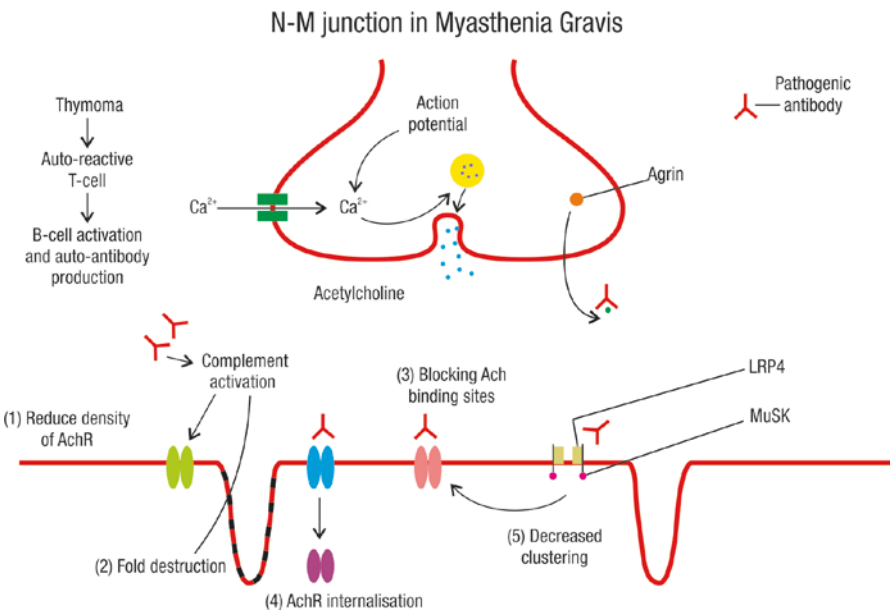

Fig. 22.6 NM junction in MG

22.4.2 Role of Thymus in MG

Thymus probably plays an important role in pathogenesis of MG. Approximately 10% of patients with autoimmune MG have a thymoma, and up to 65% of patients have associated thymic hyperplasia. In younger patients (less than 40–50 years old at disease onset), thymus contains many germinal centres. Thymus contains AchR-primed T cells, myoid cells that express AchR on surface and lymphocytes that contain AchR-specific antibodies. Thymectomy improved clinical outcomes over a 3-year period in patients with nonthymomatous MG. In contrast, thymus in MuSK MG is normal or very mildly abnormal (Vincent 2002; Ha and Richman 2015; Gilhus et al. 2016; Vincent and Leite 2005 and Wolfe GI 2016).

22.5 Investigations

There are many conditions which mimic MG, and prolonged use of medications or surgical thymectomy has potential of side effects. Hence, it is important to make a definite diagnosis of MG (Drachman 2016a, b). Diagnostic tests for MG are as follows:

22.5.1 Ice-Pack Test

Application of ice pack for 2 min on the ptotic eyelid improves ptosis in MG patients. Sensitivity and specificity of ice-pack test are 89 and 100%, respectively. It is a bedside test which is cheap, easy, requires no special instruments, requires no

monitoring for side effects and is easy to interpret. It is often argued that improvement in ptosis during ice-pack application is caused by rest. In a study, mean improvement in ptosis with ice test as against rest without cold application was 4.5 mm and 2 mm. Thus, ice-pack test improves ptosis significantly when compared to rest alone (Kubis et al. 2000 and Larner 2004a, b).

22.5.2 Repetitive Nerve Stimulation (RNS)

Sensitivity of RNS varies with the topography of muscle weakness, the disease form, disease severity and selection of muscles for testing. Decrement more than 10% is considered significant and fourth or fifth stimulus has lowest amplitude (Fig. 22.7). Sensitivity of RNS ranges from 33 to 67% in ocular MG and 80 to 98% in generalised MG. Nasalis and anconeus revealed maximum sensitivity in ocular MG, while trapezius is most likely to show abnormal results in generalised MG. Diagnostic sensitivity can be improved by bilateral stimulation and increasing the number of tested muscles. In MuSK MG, RNS is abnormal in 60% of patients when facial and distal upper extremity muscles were tested and 20% when distal upper limbs were chosen (Witoonpanich et al. 2011; Guptill et al. 2011 and Costa et al. 2004 and Bou Ali et al. 2017).

22.5.3 Tensilon or Neostigmine Test

Administration of edrophonium [2–10 mg IV] or neostigmine produces improvement in patients with MG. The positivity of edrophonium test ranges from 60 to 86% in ocular MG and 84 to 95% in generalised MG. In a case series, positivity rate of neostigmine test was 93% in ocular MG and 97% in generalised MG. Complications after edrophonium test are rare, but occurrence of

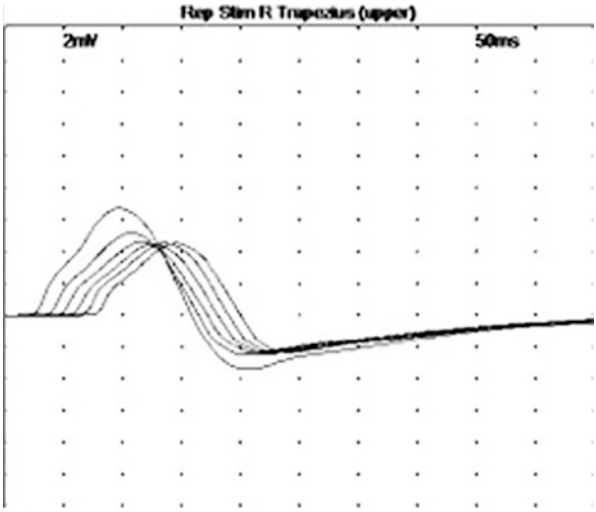

Fig. 22.7 RNS demonstrating significant decremental response in MG (Courtesy Dr. khushnuma Mansukani, Bombay Hospital, Mumbai)

bradyarrhythmias, respiratory failure and syncope has been reported. In a large case series of MuSK MG, neostigmine test was abnormal in 75% of patients, and patients often develop cramps and fasciculations (Pascuzzi 2003; Guptill et al. 2011 and Patil et al. 2016a, b).

22.5.4 Antibody Tests

AchR antibodies are the most common antibodies detected in MG patients. In a systematic review, the sensitivity of AchR antibodies in diagnosis of ocular MG and generalised MG was 44% and 80–96%, respectively. The specificity of AchR for diagnosis of MG was extremely good (98–99%). Hence, presence of antibodies is more important than absence of antibodies in establishing diagnosis of MG (Benatar 2006). Positivity of AchR antibodies ranges from 84 to 93% in large case series from India (Patil et al. 2016a, b; Singhal et al. 2008 and Khadilkar et al. 2014). In a proportion of patients who tests negative for AchR antibodies, antibodies to MuSK and LRP4 antigen can be detected. Presence of anti-RyR and anti-titin antibodies is also encountered in a proportion of patients, alongside more conventional antibodies.

22.5.5 SFEMG

It is the most sensitive diagnostic test available for MG. It is abnormal in 99% of patients with generalised MG and in 97% of patients with ocular MG. Extensor digitorum communis can be chosen when generalised MG is suspected, and frontalis or orbicularis oculi should be studied when ocular MG is suspected (Juel 2012).

Chest CT should be performed in patients with MG as up to 10% of patients with MG have thymoma associated MG. MG coexists with other autoimmune disorders, particularly thyroid disorders. Hence, workup for autoimmune thyroid conditions and other autoimmune disorder such as rheumatoid arthritis, systemic lupus erythematosus and dermatological conditions such as vitiligo should be undertaken in MG patients, when it is clinically appropriate (Juel and Massey 2007 and Drachman 2016a, b). Investigations such as complete blood count, blood sugar, renal function tests, liver function tests and chest X-ray need to be done at starting and then monitoring of immunosuppressant agents.

22.6 Differential Diagnosis

It is important to recognise disorders that closely mimic ocular and generalised MG for selection of appropriate treatment and to avoid unnecessary use of prolonged medications. Such disorders with their key differentiating features are described in Table 22.3.

Table 22.3 Differential diagnosis of MG with their key distinguishing features

Subtypes of MG	Diseases	Key distinguishing features
Ocular MG	Thyroid ophthalmopathy	Presence of ptosis, lid lag, lid retraction, periorbital oedema and lack of ptosis. Severe illness can lead to vision impairment. Lateral rectus is often spared in thyroid ophthalmopathy
	Chronic progressive external ophthalmoplegia (CPEO)	Slowly progressive, symmetrical, nonfluctuating and nonfatigable ptosis, early slowing of saccades and ophthalmoparesis. Associated features are retinal degeneration; ataxia and cardiac involvement are seen in CPEO
	Multiple cranial neuropathies	Weakness in distribution of cranial nerves, pupillary involvement, absence of fluctuations and fatigability associated pain suggests pseudotumour or compressive lesions
	Miller–Fisher syndrome (MFS)	Pupillary involvement, depressed reflexes, absence of decrement on RNS and rapid progression of illness with monophasic course favour MFS.
Generalised MG	Lambert–Eaton myasthenic syndrome (LEMS)	Mild and less common ocular and bulbar involvement, prominent limb weakness at onset, pain in limbs, autonomic dysfunction, sensory complaints, transient improvement with exercise, depressed reflexes, more than 100% increment on RNS and presence of tumours such as small cell lung carcinoma favour LEMS
	Amyotrophic lateral sclerosis	Bulbar onset ALS is a close differential of MuSK MG. Tongue atrophy with fasciculations, sparing of extraocular muscles, presence of jaw jerk, exaggerated gag reflex and pseudobulbar affect point to bulbar onset ALS
	Polymyositis	Absence of ocular involvement, absence of fatigability and fluctuations, muscle pains, systemic features like fever, skin rash, joint pains, high creatine kinase values and absence of decrement on RNS are features of polymyositis
	Congenital myasthenic syndrome (CMS)	First to second decade onset, ptosis, ophthalmoparesis, recurrent episodes of bulbar and respiratory weakness, affection of family members, absence of AchR and lack of response to acetylcholine esterase inhibitors favour CMS. Some subtypes of CMS have severe limb girdle weakness without ocular and bulbar involvement, sluggish pupillary response, distal upper limb weakness, after CMAPs while testing motor nerves
	Oculopharyngeal muscular dystrophy (OPMD)	Fifth decade or later onset, symmetrical ptosis, ophthalmoparesis, history of affection of family members, slow progression, absence of fatigability and fluctuations favour OPMD
	Botulism	Acute onset, rapid progression, pupillary paralysis, diarrhoea and incremental response on RNS occur in botulism

22.7 Management

MG is one of the best understood and probably most treatable autoimmune neurological disorders. Severity of MG varies from mild illness such as ocular MG to life-threatening myasthenic crisis. MG often causes severe disability and, if untreated, can be fatal. Over the last few decades, introduction of increasing number of immunotherapies and advances in critical care have had a significant impact on morbidity and mortality in MG. With optimal therapy, most patients can return to productive lives, and mortality is now a rarity (Drachman 2016a, b and Skeie et al. 2010 and Silvestri and Wolfe 2012). There are no evidence-based guidelines, and treatment has to be individualised for each patient (Díaz-Manera et al. 2012). Treatment strategies depend on age of the patient, presence of bulbar and respiratory weakness, rate of progression, associated thymoma and side-effect profile of the medications. Different modalities of treatment for MG are summarised in Table 22.4.

General comments and principles of drug therapy are as follows: Initial deterioration with corticosteroids needs to be anticipated and factored in. In severely symptomatic patients who are admitted and are on ventilatory support, full doses of steroids can be instituted as the worry of initial worsening has been taken care of, by the ventilatory support. Mild and moderately symptomatic patients should preferably be started

Table 22.4 Various treatment modalities and their roles in management of MG

Medications	Role in MG
Symptomatic treatment	
Acetylcholinesterase inhibitor (AChE): pyridostigmine	It is the first-line treatment for all forms of MG. At times, mild forms of ocular MG can be managed alone with pyridostigmine alone. AChEs are to be cautiously used in MuSK MG, as patients can have AChE sensitivity (Skeie et al. 2010)
Beta-adrenergic agonists: salbutamol, terbutaline and ephedrine	These agents can be effective as adjunct symptomatic therapy in MG. It is not routinely used because it is less efficacious than pyridostigmine and can produce serious side effects (Soliven et al. 2009)
Rapidly acting immunotherapies (rescue agents)	
Plasmapheresis (PE)	Many case series report short-term benefit from plasmapheresis in MG, particularly in myasthenic crisis. Its effects start rapidly within days and last for few weeks. PE can be used during myasthenic crisis; preoperatively before thymectomy or any other surgery; as a bridge to slower acting immunotherapies in severe presentations. The use of repeated PE is not recommended for continuous immunosuppression (Gajdos et al. 2002 and Skeie et al. 2010)
Intravenous immunoglobulins (IVIg)	In exacerbation of MG, one trial showed benefit of IVIg over placebo. There is insufficient evidence to determine efficacy of IVIg in chronic MG. There is no evidence to conclude that PE works faster than IVIg during crisis, and a choice between two should be based on cost, availability and side-effect profile (Gajdos et al. 2012 and Skeie et al. 2009)

Table 22.4 (continued)

Medications	Role in MG
Chronic immunotherapies	
Corticosteroids (CS): prednisolone is preferred agent	About 60–80 mg daily CS showed improvement in more than 80% of patients with MG (Pascuzzi et al. 1984). It is most effective oral immunotherapy for MG (Silvestri and Wolfe 2012). It is first choice drug when immunotherapy is required. Initial high dose of CS can temporarily worsen MG symptoms. It may hence be started at low dose (10–25 mg) and then slowly increased as per clinical response to a maximum of 60–80 mg when required. Once a desirable response is achieved, CS should be tapered by 5 mg per 2 weeks to maintenance dose of 5 or 10 mg alternate day. In severe illness, along with rapidly acting immunotherapy, high-dose steroids (60–80) can be started (Skeie et al. 2010 and Silvestri and Wolfe 2012)
Azathioprine (AZA)	Immunosuppressive effects of AZA alone and in combination with steroids have been observed in few studies (Mantegazza et al. 1988 and Witte et al. 1984). AZA has long been considered to be the first choice 'steroid-sparing' agent. Onset of therapeutic effect is delayed by 4–12 months, and hence, it has to be overlapped with steroids (Silvestri and Wolfe 2012 and Skeie GO 2010)
Mycophenolate mofetil (MMF)	Equivocal results regarding efficacy of MMF in MG are available. Two randomised controlled trials have failed to show any additional benefit of MMF in patients who were on steroids (Sanders and Siddiqi 2008). However, a retrospective study has demonstrated benefit of MMF after 6 months, both in combination and as monotherapy (Hehir et al. 2010). At present, it can be used in patients, who are intolerant or unresponsive to AZA (Skeie GO 2010 and Burns et al. 2015)
Cyclosporine A (CyA) and Tacrolimus	In a placebo-controlled trial, CyA showed greater reduction in strength than placebo in patients with steroid-dependent MG. However, side effects caused 35% to discontinue medications (Tindall et al. 1993). Evaluation of available evidence showed beneficial evidence of tacrolimus in reducing disease burden in both steroid-dependent and new cases (Cruz et al. 2015). Tacrolimus has produced rapid improvement in patients with anti-RyR antibodies. Hence, both agents can be considered in patients intolerant or unresponsive to AZA. Side-effect profile of tacrolimus is more favourable than CyA (Skeie GO 2010)
Cyclophosphamide (CP)	Intravenous pulse doses of CP have shown benefit in patients with poor disease control on steroids or steroid-sparing agents (AZA, MMF, CyA). CP has not only improves muscle strength but also helps in reduction in dosages and stoppage of steroids, pyridostigmine and steroid-sparing agents. Side effects are managed symptomatically and rarely required discontinuation of CP. Mean duration of remission is approximately 20 months (Nagappa et al. 2014, De Feo et al. 2002 and Skeie GO 2010)

(continued)

Table 22.4 (continued)

Medications	Role in MG
Methotrexate	In a randomised, double-blind placebo control trial, methotrexate showed reduction in steroid dosages in patients with MG, but there was no improvement in strength. Methotrexate was well tolerated in these patients (Pasnoor M 2016). Hence, methotrexate can be used in patients who do not respond to other steroid-sparing agents
Rituximab	A number of case series have shown significant benefit of rituximab in patients with severe generalised MG which is refractory to multiple immunosuppressive agents. It has shown efficacy and long-term benefit in MuSK MG. Hence, it can be considered in severe forms of refractory AchR and MuSK MG. Unlike other agents, it has rapid onset of action (Iorio et al. 2015, Sudulagunta et al. 2016 and Gotterer and Li 2016)
Leflunomide	A single study is available to document benefit of leflunomide in terms of reducing steroid dosage and improving muscle strength. It was well tolerated without any significant side effects. Hence, it may form an option in patients with steroid-dependent MG, who are intolerant to AZA (Chen et al. 2016)
Surgical treatment	
Thymectomy	As thymus is strongly implicated in initiating immune response in MG, thymectomy has been a component of management of MG Thymoma MG: Thymectomy should be done in all cases and has shown benefit in early-onset cases Early-onset MG: A randomised control trial in patients with nonthymomatous MG has shown reduction in steroid dosage, immunosuppressive medications and fewer exacerbations rates with thymectomy and steroids group than patients taking steroids alone (Wolfe GI 2016) Late-onset MG: This group is less responsive or nonresponsive to thymectomy. However, in patients in age group of 50–65 years with severe disease and thymic hyperplasia, thymectomy may show benefit similar to early-onset MG. Presence of anti-RyR antibodies probably indicates that no response will occur to thymectomy (Gilhus et al. 2016) MuSK and LRP-4 MG: In absence of thymic pathology in these subgroups and very scarce evidence, thymectomy is not recommended at the present time. Similarly in ocular and seronegative MG, there are no data to support use of thymectomy (Gilhus et al. 2016)

on small doses, beginning at 5–10 mg of prednisolone per day and gradually increased over few weeks, depending upon the tolerance and requirements of the individual. This reduces the chances of deterioration. Addition of the second immunosuppressant should be attempted once the steroids have begun working and patient has improved. Simultaneous introduction of the second agent does not add any further benefit, rather increases the issues of unwanted effects. Remission often results after an unpredictable period, which could be prolonged. Pharmacological remissions are far more common than true remissions and only a minority of individuals can be taken completely off medications and remain well. It is also important to realise that the

recurrence potential after a remission is ever present and hence regular follow-ups are necessary even in those who have apparently stabilised or remitted.

Management of generalised AchR antibody-positive MG differs from one person to another. The aim of therapy is to relieve from fatigable weakness, long-term disease stabilisation and prevention of myasthenic crisis. A broad framework to choice of treatment strategies has been outlined in Table 22.5.

Abovementioned guidelines produce satisfactory results in most patients with AchR antibody-positive generalised MG. However, certain subgroups or situations require different protocols. Such special circumstances and their management are summarised in Tables 22.6 and 22.7.

Table 22.5 Stepwise approach to management of a patient with generalised AchR antibody positive MG

Step 1: If patient has presented with severe bulbar weakness and impending respiratory failure at onset, then use one of rapidly acting immunotherapies + high-dose steroids + supportive management
Step 2: When patient has improved, then start AChE and taper steroids to maintenance dose; AChE + low-dose steroids to be initiated in mild to moderate illness at onset
Step 3: Evaluate for need of thymectomy and perform procedure if indicated (refer Table 22.4)
Step 4: Assess for response and tailor steroids doses according to response
Step 5: Consider steroid-sparing agent irrespective of desirable improvement achieved or not as MG has fluctuating course. AZA is considered 'first-line' steroid-sparing agent
Step 6: Assess response to AZA and steroids. If patient improves or remission occurs, then taper steroids to minimum doses, taper and discontinue AChE if possible and continue AZA in maintenance dosages. AZA has slower onset of action and it should be continued for substantial period before considering it to be ineffective
Step 7: If Patients are intolerant or less responsive to AZA, then use 'second-line' steroid-sparing agent such as MMF, CyA or tacrolimus depending on side-effect profile and assess response
Step 8: If patients are intolerant or less responsive to above agents, then consider CP or rituximab. Both have advantage of relatively rapid onset of action than other immunosuppressive agents. Leflunomide and methotrexate can be used as alternative agents
Step 9: In case of worsening of illness, steroids can be used in incremental doses along with AChE. In severe cases, rapidly acting immunotherapies should be considered

Table 22.6 Special circumstances and their treatment strategies

Special circumstances	Treatment strategies
Ocular MG	Start with AChE. If AChE alone is unsuccessful, then use low-dose steroids and use in incremental doses, till good control of symptoms is achieved. If steroids are needed for long term, then consider AZA as steroid-sparing agent. This may prevent myasthenia generalisation. Thymectomy is indicated if ocular MG is associated with thymoma; otherwise, its role is controversial (Kerty et al. 2014)
MuSK MG	MuSK MG shows AChE sensitivity, high likelihood of side effects and poor response to AChE. Most patients need two or more immunosuppressive drugs. Rituximab produces sustained response and plasmapheresis is superior to IVIg in treating acute exacerbations (El-Salem et al. 2014, Bouwyn et al. 2016 and Guptill et al. 2011)

(continued)

Table 22.6 (continued)

Special circumstances	Treatment strategies
Seronegative MG	Treatment strategies are similar to AchR-positive generalised MG, except that there is no role of thymectomy in seronegative MG
Myasthenic crisis	Common causes of crisis are infections, surgery and tapering of medications. Mechanical ventilation in impending respiratory failure; avoid antibiotics or other medications that can exacerbate MG. AChE can increase oral secretions and, hence, should be used at minimum tolerable doses; high-dose steroids should be given if infection is under control; IVIg or plasmapheresis should be used as rescue therapy
Pregnancy	If MG is under good control before pregnancy, then it is most likely that patient will remain stable throughout pregnancy. AChE is first-line treatment during pregnancy. Prednisone is the immunosuppressive agent of choice during pregnancy. AZA and CyA are relatively safe than MMF, methotrexate and CP in expectant mothers who are not satisfactorily controlled with or cannot tolerate steroids. Plasmapheresis or IVIg can be used as rescue therapy in severe illness during pregnancy. Avoid magnesium sulphate if patients develop eclampsia. Babies born to myasthenic mothers can develop transient weakness and may require critical care support (Sanders et al. 2016)
Refractory MG	Patients in whom routine immunotherapy cannot be lowered without clinical relapse, in whom symptoms control is poor with these medications, and who require frequent rapidly acting immunotherapies or develop severe side effects of medications are grouped as refractory MG. Rituximab, CP and thymectomy can be offered to such patients. There is single case report of improvement in symptoms with bone marrow transplantation in refractory MG. Eculizumab infusions have shown improvement in small number of patients with refractory MG (Silvestri and Wolfe 2014a, b)

Table 22.7 List of commonly used medications to be cautiously used in patients with MG

Immunosuppressants	Corticosteroids and interferon
Antibiotics	Fluoroquinolones, aminoglycosides, macrolides, ampicillin, vancomycin, clindamycin and imipenem
Drugs used in surgery	Atracurium, rocuronium, pancuronium, enflurane, isoflurane, lidocaine and xylocaine
Cardiovascular drugs	Calcium channel blockers, beta blockers and magnesium
Anti-rheumatic agents	Chloroquine and penicillamine
Anticonvulsants	Phenytoin
Analgesics	Opioids
Antipsychiatric drugs	Lithium
Miscellaneous	Iodinated contrast agents, glaucoma eye drops, botulinum toxin and magnesium-containing laxatives

For further details, one may refer to following website [http://www.myasthenia.org/LinkClick.aspx?fileticket=JuFvZPPq2vg%3D]

22.8 Prognosis

The natural history of illness is complicated by fluctuations in disease activity ranging from spontaneous remissions to exacerbations (Khadilkar et al. 2014). Increasing age and respiratory muscle weakness are two main contributors to MG crisis and mortality (Farrugia and Vincent 2010). With recent advances in immunotherapies and critical care, there is increased survival and improved quality of care in most patients with MG (Dalakas 2015). In a long-term observational study, occurrence of spontaneous remission was rare, and most patients needed long-term immunosuppression (Khadilkar et al. 2014). Patients with late-onset MG, history of thymectomy and ocular-only disease at maximum severity had optimal outcome irrespective of their antibody status (Andersen et al. 2016).

22.9 Case Study

Clinical details: A 30-year-old man presented with history of fatigable ptosis, diplopia, bulbar and limb weakness over a period of 3 months. Investigations revealed significant decrementing response on RNS and elevated AchR antibodies; confirming generalised AchR positive MG. Thyroid levels were normal and HRCT thorax showed thymic hyperplasia. Due to significant respiratory distress and bulbar weakness, patient required invasive ventilatory support. He was treated with PE and 1 mg/kg of corticosteroids. After 5 cycles of PE, patient showed significant improvement and was extubated. He still had fatigable ptosis, diplopia, facial and mild limb weakness but was ambulatory. A second immunosuppressant was now considered. Selection of the immunosuppressive agents has to be individualised. AZA and MMF forms the first choice ‘steroid-sparing agent’.

2011: MMF was started at dose of 500 mg once a day and patient was already on 1 mg/kg steroids. Over the next 10–15 days, patient developed reduction in white blood cell count. Considering idiosyncratic response to MMF, it was discontinued. Meanwhile, symptoms worsened; the patient developed severe weakness and needed re-intubation and ventilatory support. Improvement occurred after 10 cycles of PE and he was extubated. Thymectomy was performed. He still had fatigable ptosis, diplopia, facial and mild limb weakness and was never asymptomatic. As benefit of PE is short lasting, patient needed steroid-sparing agent to act before recurrence of symptoms occurs.

2011–2013: Pulse CP was now used owing to its faster onset of action. Pulse CP was given once/monthly for 6 months, once/bimonthly for 3 cycles, and once in 3 months for last 3 cycles, and steroids was tapered gradually. Patient had remarkable improvement, and over a period of 1.5–2 years, remission was achieved. AZA was started at dose of 50 mg OD, when 12 cycles of pulse CP ended. Gradually, AZA was increased to 150 mg per day with monitoring of blood counts and liver function tests along with 5 mg per day steroids. Symptoms worsened at 6–7 months

after the onset of AZA. Steroids were slowly titrated upwards up to 40–50 mg per day, but the patient did not have significant improvement.

2014: He developed upper respiratory tract infection and subsequently developed crisis. He required invasive ventilatory support and 7 cycles PE. AZA 150 mg/day was continued with 1 mg/kg steroids. Symptoms were stable on these medications, but symptoms worsened after tapering of steroids. He developed steroid facies and had scar due to multiple tracheostomies and thymectomy (Fig. 22.8). He developed severe ptosis, facial and limb girdle weakness which warranted change of steroid-sparing agent.

2015: Tacrolimus was started at 1 mg and increased to 2 mg per day. He showed gradual improvement and became ambulatory but still had residual weakness. Steroids were gradually tapered to 10 mg per day. After a period of 6 months,

Fig. 22.8 Ptosis, puffiness of face due to steroids use, tracheostomy and thymectomy scar in a patient with severe manifestation of MG

symptoms worsened despite tacrolimus levels being close to upper limit of normal. Limb girdle and facial symptoms were severe enough to cause significant disability.

2016: Most agents were now used without any long-term benefits and symptoms deteriorated with steroid taper, causing severe disabling symptoms and recurrent crisis. Rituximab has been observed to result in improvement in such scenario, where the use of standard steroid-sparing agents did not yield benefits. Rituximab 500 mg every week infusion for 4 weeks was given. He showed remarkable improvement in symptoms, and follow-up 6 monthly infusions were administered after monitoring of CD19 counts.

This case illustrates the issues in long-term management of resistant myasthenia. The choice of steroid-sparing agents has to be individualised based on symptoms control and resolution of disability.

Key Points

When to suspect

- Fatigable ptosis, diplopia, chewing and swallowing difficulties
- No other LMN signs
- Improvement with rest

How to diagnose

- Ice-pack test
- Tensilon or neostigmine test
- Decrementing response, SFEMG
- Antibodies: AchR, MuSK, LRP4
- Chest CT for thymus

How to treat

- PE or IVIg as rescue therapy
- Intensive care for crisis
- Long-term immunosuppressants

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Lambert–Eaton Myasthenic Syndrome 23

23.1 Introduction

LEMS is an autoimmune disorder affecting the neuromuscular junction. It is characterized by progressive proximal weakness, fatigue, depressed tendon reflexes, autonomic dysfunction and characteristic electrophysiological response to repetitive nerve stimulation (RNS). It is caused by autoantibodies against voltage-gated calcium channels (VGCC) located on presynaptic terminals of neuromuscular junction (Gilhus 2011). This disorder was initially described as atypical myasthenia in patients suffering from lung carcinoma, but we now know that a proportion of patients having LEMS do not have any tumour in the body. Clinical, genetic and serological markers help to differentiate tumour-associated LEMS (T-LEMS) from non-tumour LEMS (NT-LEMS), and these features have been validated as Dutch–English LEMS Tumour Association Prediction (DELTA-P) score (Hülsbrink and Hashemolhosseini 2014 and Titulaer et al. 2011a, b, c). Management is based on anticancer therapy for patients with T-LEMS in conjunction with immunosuppression and symptomatic treatment. Therapy of NT-LEMS is based on immunosuppression and symptomatic treatment (Maddison 2012).

23.2 Epidemiology

LEMS is a rare autoimmune disorder and its incidence is less than one per one million populations (Titulaer et al. 2011a, b, c and Matsumoto 2016). Epidemiology differs for both T-LEMS and NT-LEMS. In about 50–60% of patients suffering from LEMS, a tumour is found, either at the time of diagnosis or later in the course of illness (Hülsbrink and Hashemolhosseini 2014). The mean age of disease onset in T-LEMS is about 60 years, and there is male preponderance, possibly reflecting smoking habits. NT-LEMS has two peaks for age at disease onset, one at around 35 years and other at 60 years. NT-LEMS do not have any sex differences (Hülsbrink and Hashemolhosseini 2014; Gilhus 2011 and Titulaer et al. 2011a, b, c). NT-LEMS has rarely been reported in children (Sanders and Guptill 2014 and Lorenzoni et al. 2010).

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Isolated case reports of LEMS have been reported from India (Ray et al. 2012; Nair et al. 2000 and Kalita et al. 1995).

23.3 Clinical Features

The clinical presentation of LEMS is characterised by a triad of progressive proximal muscle weakness, depressed tendon reflexes and autonomic dysfunction. Patients complain of fatigue and muscle pains, and at times their symptoms tend to be out of proportion to the degree of muscle weakness. Details of clinical features are summarised in Table 23.1 (Sanders and Guptill 2014 and Titulaer et al. 2011a, b, c).

Table 23.1 Clinical features of LEMS

Weakness	Weakness of lower or upper limbs occurs in nearly all patients. Weakness begins in proximal lower limb and progresses in a caudocranial pattern to involve proximal upper limbs. Ocular and bulbar muscles are affected at later stages of illness. Weakness of distal leg and respiratory muscles is uncommon but can be seen in T-LEMS. Synaptotagmin 2 mutations can have features of presynaptic neuromuscular junction resembling LEMS and motor neuropathy. These patients have prominent foot deformities such as hammer toes and pes cavus (Herrmann et al. 2014)
Depressed tendon reflexes and 'postexercise facilitation'	Hyporeflexia or areflexia is found in 90–100% of patients with LEMS. Immediately after muscle contraction, a short-lasting increase of reflexes can be observed in 40% of patients with LEMS. This phenomenon is known as 'postexercise facilitation' and is very suggestive of LEMS (Hülsbrink and Hashemolhosseini 2014)
Autonomic dysfunction	Occurs in more than 60% of patients within 3 months of onset and more than 90% of patients develop autonomic dysfunction in later stage of illness (Titulaer et al. 2011a, b, c). Dry mouth is most common symptom, and other features are constipation, postural hypotension, decreased libido, altered sweating and, rarely, blurred vision due to pupillary paralysis (Titulaer et al. 2011a, b, c, Sanders and Guptill 2014 and Lorenzoni et al. 2010)
Fatigue	Patients complain of constant muscle fatigue and reduced motor endurance. Curiously, transient improvement in muscle strength occurs immediately after exercise, but weakness worsens on prolonged exercise (Sanders and Guptill 2014 and Sanders 2003)
Ocular and bulbar weakness	Ocular and bulbar symptoms are less common as compared to MG. In a large case series, frequency of ocular and bulbar features was 30% within 3 months of onset. At 12-month follow-up, 50% of patients had ocular and bulbar features. Most patients with ocular involvement have ptosis and mild ophthalmoparesis. On extremely rare occasions, patients have ptosis and fatigable diplopia at onset of illness. This subgroup is known as myasthenia gravis Lambert–Eaton overlap syndrome (MLOS) (Oh 2016, Titulaer et al. 2011a, b, c and Rattananan et al. 2016)
Other features	Few patients are known to develop sensory dysfunction, and cerebellar ataxia occurs in small proportion of patients, particularly with T-LEMS (Matsumoto 2016 and Lorenzoni et al. 2010)

Table 23.2 DELTA-P score

	Categories	Within 3 months of onset	Score
D	Dysarthria, dysphagia, chewing, neck weakness: bulbar weakness	Absent Present	0 1
E	Erectile dysfunction	Female Male: absent Male: present	0 0 1
L	Loss of weight	Absent or <5% ≥ 5%	0 1
T	Tobacco use at onset	Absent Present	0 1
A	Age of onset	<50 years ≥50 years	0 1
P	Karnofsky performance score	70–100 0–60	0 1

More than 50% LEMS are associated with tumours. Small-cell lung carcinoma (SCLC) accounts for about 90% of tumours in patients with T-LEMS. Other tumours that can be associated with LEMS are lymphoma, leukaemia, prostate carcinoma, breast, laryngeal carcinoma, etc. (Matsumoto 2016). Features of LEMS often precede manifestations of underlying tumour. Presence of tumour in patients with LEMS has a huge impact on treatment and prognosis. As T-LEMS and NT-LEMS differ in clinical presentation, DELTA-P score has been validated to predict presence of SCLC in a patient in LEMS (Hülsbrink and Hashemolhosseini 2014 and Titulaer et al. 2011a, b, c). DELTA-P score has been described in Table 23.2.

The probability for SCLC can be calculated at the time of diagnosis of LEMS and varies from 0 to 2.6% with a DELTA-P score of 0–1, up to 83.9 to 100% with a score of 3–6 (Titulaer et al. 2011a, b, c).

23.4 Pathophysiology

Voltage-gated calcium channels (VGCCs) are located on presynaptic neuronal cell membrane, mediate calcium influx and play an important role in release of acetylcholine (Ach) release into synaptic terminals. In LEMS, autoantibodies against VGCC lead to reduction in quantal release of Ach. Muscle weakness and autonomic dysfunction are caused by VGCC antibodies that impair Ach release from presynaptic nerve terminals, parasympathetic and sympathetic neurons. In experimental animals, a direct pathogenic effect of these antibodies has been observed after direct injection of VGCC autoantibodies. VGCC has been divided into many subtypes according to tissue where they are detected, pharmacological properties and protein structure. In LEMS, antibodies are found the P/Q and Ca_v 2.1 subtype of VGCC. A genetic susceptibility has been established for NT-LEMS and is associated with HLA-B8, DR3 and DQ2 (Gilhus 2011).

23.5 Investigations

Investigations are necessary to confirm diagnosis of LEMS and also detect presence of associated illness, in addition to LEMS. Following tests should be done.

23.5.1 Electrophysiology

The classical electrophysiological findings of LEMS are a low compound muscle action potential (CMAP) at rest, a decremental response to low-rate stimulation (LRS) and an incremental response on high-rate stimulation (HRS) (Fig. 23.1). CMAPs of abductor digiti minimi (ADM), abductor pollicis brevis (APB), extensor digitorum brevis (EDB) and trapezius muscles are recorded at rest. CMAPs are usually low in most of patients with LEMS. On LRS at 2–5 Hz, decrement >10% can be demonstrated in more than 80% patients with LEMS. HRS at 50 Hz can produce increment response up to 1800% but >100% increase in motor amplitudes is considered to be diagnostic of LEMS. The sensitivity and specificity of 60% increment are 97% and 99%, respectively, but it should be kept in mind that incremental response up to 94% has been observed in some patients with myasthenia gravis (MG). Considering 60% increment as suggestive is helpful in seronegative LEMS as they tend to show lesser incremental response than seropositive cases. CMAP after 10–30 s of exercise can be compared to CMAP at rest to demonstrate postexercise facilitation (PEF). PEF > 100% is seen in majority of patients with LEMS. ADM is the most frequently studied muscle for demonstrating electrophysiological changes of LEMS. Needle electrode examination (NEE) may show myopathic potentials, but presence of this triad is considered diagnostic of LEMS (Titulaer et al. 2011a, b, c; Oh et al. 2005; Oh et al. 2007; Mills 2005 and American Association of Electrodiagnostic Medicine 2001).

23.5.2 Serological Markers

Antibodies against P/Q-type VGCC are found in 85–90% of patients with LEMS with a specificity of nearly 100%. In 1–4% of patients with SCLC without neurological dysfunction, these antibodies can be seen. Rarely, antibodies against N-type VGCC can be seen in absence of P/Q-type VGCC antibodies. Antibodies against other proteins, e.g. SOX1, muscarinic acetylcholine receptors and synaptotagmin, have uncommonly been described in seronegative patients. Antibodies against SOX1 are known to exist in some T-LEMS (Nakao et al. 2002; Titulaer et al. 2011a, b, c).

23.5.3 Imaging

Screening for tumours especially SCLC should be done in all patients. Initially, CT thorax is recommended, and if negative then, positive emission tomography (PET) scan of the whole body should be done. When primary screening is negative, then

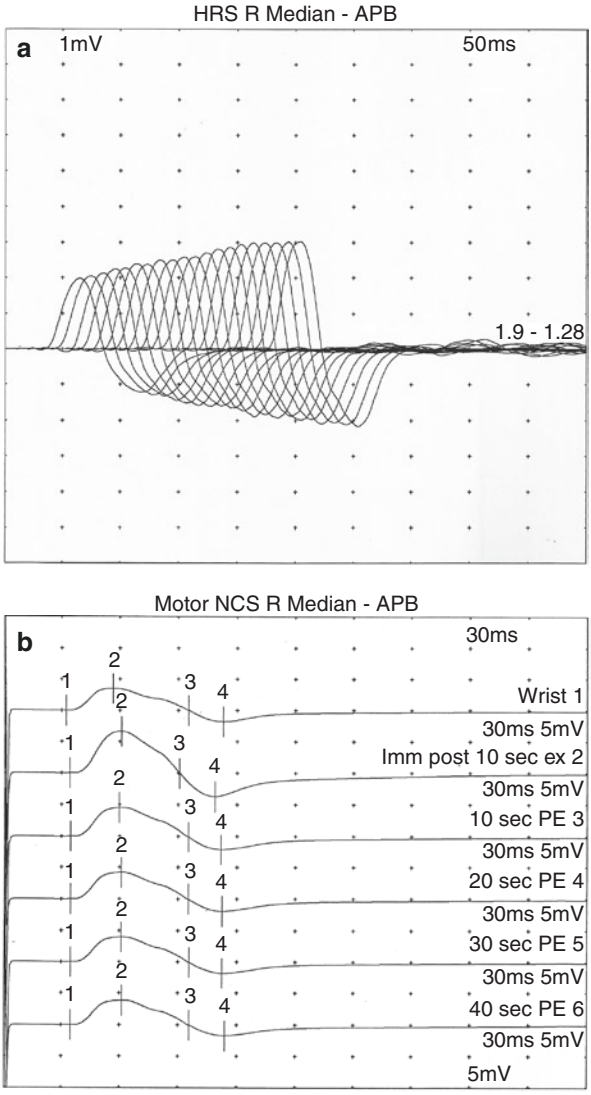

Fig. 23.1 (**a**) High-frequency repetitive stimulation (50 Hz) showing an increment in a patient of LEMS and (**b**) short exercise test in LEMS: Low amplitude baseline CMAP in trace 1; immediately following a 10 s exercise, the CMAP improves by 100%, trace 2, and subsequent traces show the CMAP amplitude dropping again (Courtesy: Dr. Khushnuma Mansukhani, Bombay Hospital, Mumbai)

patients should be screened every 6 months up to a period of 2 years (Titulaer et al. 2011a, b, c).

The presence of clinical features combined with either VGCC antibodies or characteristic electrophysiological features or both are required for diagnosis of LEMS. Clinical features consist of triad of proximal muscle weakness, depressed tendon reflexes and autonomic dysfunction. Presence of low CMAP amplitude, decrement on LRS and increment on HRS form the electrophysiological triad of LEMS (Titulaer et al. 2011a, b, c).

23.6 Differential Diagnosis

It is important to differentiate LEMS from its mimics as treatment and prognosis of patients with LEMS is entirely different. Closest differential of LEMS is MG. Differential diagnosis of LEMS and their key differentiating features are tabulated below in Table 23.3.

23.7 Management

Therapy for LEMS depends on whether it is associated with underlying tumour or not and has to be individualised. The following management strategies for LEMS can be used.

23.7.1 Symptomatic Treatment

Symptomatic therapy helps to deal with reduced quantal release of Ach or decreased Ach in synaptic terminals. 3,4-Diaminopyridine (3,4-DAP) is the mainstay of symptomatic treatment. It blocks presynaptic voltage-gated potassium channels, prolongs the duration of presynaptic action potential and increases Ach release. It helps to improve weakness and CMAP amplitudes over days, and the benefit has been demonstrated in various randomised control trials (Gilhus 2011 and Keogh et al. 2011). Common side effects are perioral tingling, acral paresthesias, fatigue, palpitations, anxiety and occasionally seizures and prolonged QTc interval. Recommended total

Table 23.3 Differential diagnosis of LEMS

Differential diagnosis	Key distinguishing features
Myasthenia gravis	In LEMS, symptoms in lower limbs occur earlier and are severe than ocular or bulbar muscles; depressed deep tendon reflexes, autonomic and sensory involvement, presence of pain, > 50% association with SCLC, characteristic electrophysiological triad and presence of anti-VGCC antibodies favour LEMS
Inflammatory myopathy (IM) presents as progressive, proximal, painful lower limb weakness and can be confused with LEMS	In IM, females are more commonly affected than males; pain in limbs rather than fatigue, jaw muscle weakness, prominent neck muscle weakness, absence of autonomic and sensory symptoms and elevated CK levels favour (IM). NEE may show myopathic potentials in both, but characteristic electrophysiological triad is absent in IM
Guillain–Barré syndrome (GBS) – limb weakness, areflexia and autonomic dysfunction can mimic LEMS	Absence of fatigue, absence of dry mouth and sparing of pupils, acute to subacute progression, features of demyelination or axonopathy, raised CSF proteins and absence of facilitation on HRS favour GBS
Lumbar canal stenosis	Prominent sensory symptoms and signs, sparing of upper limbs and neck, preserved autonomic function except bladder and neurogenic denervation on NEE favour lumbar canal stenosis

dose is 80 mg per day in four divided doses as a tendency to develop seizures increases beyond 80 mg. Amifampridine is a phosphate salt of 3,4-DAP and has been recently approved for treatment of LEMS (Titulaer et al. 2011a, b, c; Sanders and Guptill 2014 and Maddison 2012). Equivocal evidence exists for effectiveness of pyridostigmine in LEMS, and addition of pyridostigmine to 3,4-DAP may provide additional benefit (Maddison 2012). In countries like India, where 3,4-DAP is not available, pyridostigmine can be used as first-line therapy for symptomatic treatment.

23.7.2 Immunosuppression

Intravenous immunoglobulin and plasma exchange have been found to be helpful in rapidly increasing muscle strength and improvement of CMAP amplitude for brief periods (Keogh et al. 2011). These modalities are useful for rapid control of symptoms and are not recommended for long-term, intermittent use (Maddison 2012). In patients who have inadequate control on symptomatic therapy, long-term immunosuppression with prednisolone and azathioprine (AZA) is considered. Similar to MG, dosages should be slowly increased based on the response. In a long-term study, AZA with steroids helped in achieving clinical remission in 43% of patients (Palace et al. 1998 and Maddison et al. 2001). In a proportion of patients with severe symptoms while on conventional oral immunosuppressive agents, rituximab have shown marked clinical benefits (Maddison et al. 2011).

23.7.3 Antitumour Therapy

As more than 50% of patients with LEMS have underlying tumours, it is important to screen for SCLC and initiate appropriate antitumour therapy. Long-term clinical and pharmacological remission has been reported in patients following successful tumour resection.

Once the diagnosis of LEMS is confirmed, symptomatic therapy is initiated, and patients should be screened for tumour with CT thorax or PET scan. If tumour is detected, then antitumour therapy can help to improve neurological symptoms. Response to symptomatic treatment should be assessed, after initiation of antitumour therapy or in cases where tumour is not detected. In cases of mild weakness, pyridostigmine can be added to 3,4-DAP. Steroids and AZA are used in patients with mild to moderate chronic impairment, while IVIg and plasmapheresis can be helpful in severe, acute presentation (Titulaer et al. 2011a, b, c and Maddison 2012).

23.8 Prognosis

More than 50% of patients with NT-LEMS achieve clinical remission, but most of patients require long-term immunosuppression (Lorenzoni et al. 2010). Disability at the time of initiating therapy is a reliable predictor for long-term outcome of LEMS

(Lorenzoni et al. 2010). The median survival time is more in patients with T-LEMS than in patients with SCLC alone (Maddison et al. 1999). Due to rarity of this disorder, there is limited data available regarding comparative efficacy of various immunosuppressive agents in LEMS (Gilhus 2011).

In the author's experience, majority of patients require prolonged immunosuppression, often going over years, and achieve limited benefits in terms of disability.

23.9 Myasthenia Gravis Lambert–Eaton Overlap Syndrome (MLOS)

Differences between MG and LEMS are well recognized. However, some patients show combined features of MG and LEMS and are grouped as MLOS. MLOS has a wider age at onset from 16 to 80 years with a mean of 47.5 years. Oculo-bulbar and limb weakness occur in more than 90% of patients. These patients have features of MG such as prominent oculo-bulbar symptoms, improvement with edrophonium and presence of acetylcholine receptor (AchR) antibody. These patients also have hyporeflexia and fulfil characteristic electrophysiological triad of LEMS, and more than 50% are positive for VGCC antibodies. Few patients of MLOS have associated tumours such as thymoma or SCLC. The best proof of existence of MLOS is combined presence of AchR and VGCC antibodies in such patients. These patients responded well to 3,4-DAP, pyridostigmine and immunosuppressant agents (Oh 2016).

23.10 Case Study

Clinical details: A 44-year-old lady presented in February of 2013 with history of slowly progressive weakness in lower limbs since 2 years. She also had ill-defined pain in both legs which was progressively increasing in severity. She was unable to neither walk without aid of a stick nor stand without support, 4 months before presentation. One month before reaching the hospital, she had been bed ridden due to severe limb weakness. She had noticed curling of toes and inability to move them freely. None of her family members suffered any neurological illnesses. On examination, power at hip and knee joints was MRC grade 2/5. Distal weakness was very severe and she was unable to move her feet and toes at all. There was hypotonia in lower limbs. Knee and ankle jerks were not elicitable and deep tendon reflexes were normal in upper limbs. Pes cavus and hammer toes were very striking (Fig. 23.2). Sensory examination was normal and plantar reflexes on both sides were mute.

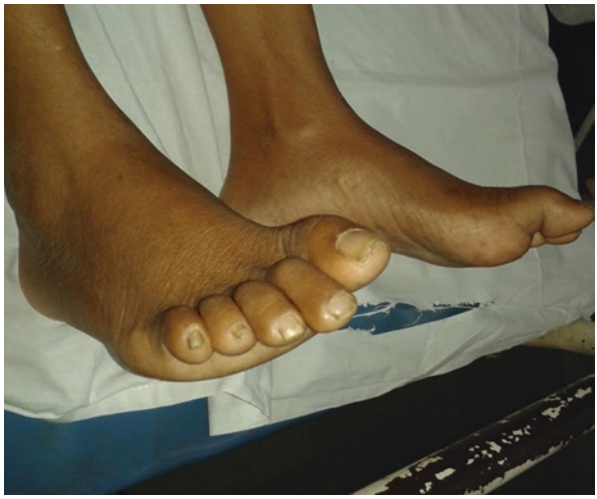

Fig. 23.2 Pes cavus and hammer toes (Courtesy: Dr. Nadir Bharucha, Bombay Hospital, Bombay and Dr. Khushnuma Mansukhani, Bombay Hospital, Mumbai)

Summary: A 44-year-old lady having progressive painful, distal more than proximal lower limb weakness, foot deformities (hammer toes and pes cavus), areflexia in lower limbs and intact sensory system.

Discussion: In view of pes cavus and distal lower limb weakness, a possibility of hereditary neuropathy was very considered, but the duration of symptoms was relatively short. As the patient had motor weakness with intact sensory system, muscle disease and neuromuscular transmission defects were also considered, but pes cavus and foot deformities are usually not associated with these disorders. Electrophysiology confirmed intact sensory system, but motor amplitudes were severely attenuated. Needle electrode examination showed myopathic pattern. Creatine kinase levels were within normal limits. Slow rate RNS showed significant decrement (28.9%), while 10 s exercise test revealed >400% increment in motor amplitudes (Fig. 23.3). Hence, diagnosis of LEMS was considered. Retrospectively, patient gave history of dry mouth but did not have history of fluctuations and fatigability. Anti-VGCC antibodies were negative. The most intriguing feature was presence of pes cavus and foot deformities. Such foot deformities and distal predominant limb weakness in LEMS have been mentioned with synaptotagmin 2 (SYT2) mutations. Patients with SYT2 mutations are known to develop presynaptic neuromuscular transmission defects, lower limb wasting and foot deformities (Herrmann et al. 2014). At the present time, synaptotagmin studies are in progress for this patient.

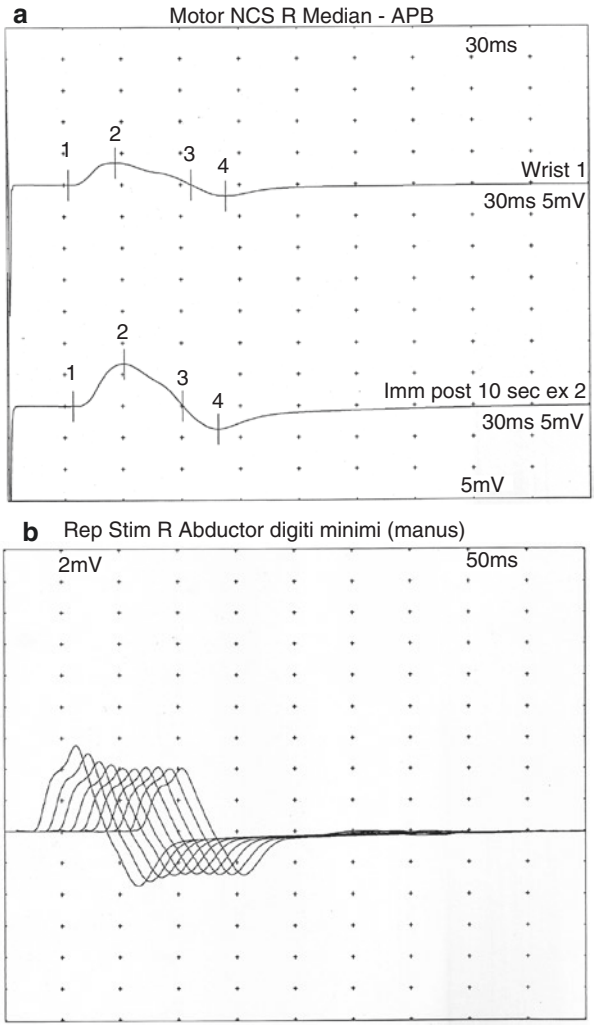

Fig. 23.3 (**a**) 10 s exercise test reveals >400% increment, and (**b**) slow rate RNS shows significant (28.9%) decrement in motor amplitudes suggestive of LEMS (Courtesy: Dr. Nadir Bharucha, Bombay Hospital, Bombay and Dr. Khushnuma Mansukhani, Bombay Hospital, Mumbai)

Key Points

When to suspect

- Limb weakness with depressed tendon reflexes
- Fluctuations
- Exercise benefit and postexercise facilitation
- Autonomic features
- Association with neoplasms

How to diagnose

- Reappearance of reflexes with exercise
- Electrophysiological triad
- Anti-VGCC antibody testing

How to treat

- Immunomodulation
- Treating malignancy when it exists

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Periodic Paralysis

24

24.1 Introduction

Skeletal muscle channelopathies form a rare group of disorders caused by mutation in genes encoding for calcium, sodium, potassium and chloride channels. Amongst these channelopathies, periodic paralysis forms the major subgroup. Primary (inherited) periodic paralyses include hypokalemic periodic paralysis (hypoKPP), hyperkalemic periodic paralysis (hyperKPP) and Andersen–Tawil syndrome (ATS), and these conditions are caused by calcium, sodium and potassium channel mutations, respectively. Autosomal dominant in inheritance, these disorders present in first to second decade of life with transient episodic weakness that is brought on by triggers and patients regain normal power in between attacks. Though they do not compromise life expectancy, recurrent episodes may lead to fixed proximal weakness and may cause considerable disabilities. It is important to recognise these disorders as frequency of episodes can be reduced with medications and by avoiding triggers and improving the quality of life. Thyrotoxic periodic paralysis (TPP) is caused by mutations in thyroid hormone-regulated potassium channel gene and can be included in the spectrum of periodic paralysis. It is important to rule out secondary causes that can cause flaccid paralysis while considering the diagnosis of primary periodic paralysis (Statland and Barohn 2013; Statland et al. 2014).

24.2 Epidemiology

Primary periodic paralyses are rare disorders. In a recent case series of genetically confirmed muscle channelopathies, the prevalence hypoKPP was 0.13, hyperKPP was 0.17 and ATS was 0.08 per 100,000 populations (Horga et al. 2013). In a case series from India, it was found that secondary causes of hypokalemic flaccid weakness were more common than hypoKPP (Mohapatra et al. 2016). TPP dominates amongst various reported periodic paralyses in India (ER and Mounika 2016; Somasila et al. 2016; K N and Sr 2016). Thyrotoxic periodic paralysis is the most

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common periodic paralysis in Asian population, while hypoKPP is in western world (Thethi et al. 2014; Statland and Barohn 2013; Elston et al. 2007). Except TPP, which has male preponderance, other periodic paralyses do not show any sex predilection (Lin 2005; Thethi et al. 2014; http://neuromuscular.wustl.edu/mtime/mepisodic.html).

24.3 Clinical Features

The cardinal presentation of these disorders is episodic weakness beginning in childhood and adolescence. Weakness mainly involves limb muscles, while facial, bulbar, ocular and respiratory muscles are largely spared. Episodes of weakness are more frequent on awakening from sleep in the morning hours. During episodes, deep tendon reflexes are diminished or absent, and sensations are normal (Statland et al. 2014). The classical triad of ATS is episodic muscle weakness in the setting of high, low or normal potassium, ventricular arrhythmias and dysmorphic facial features (Sansone et al. 1997; Tawil et al. 1994). Key features of various periodic paralyses are tabulated in Table 24.1.

Table 24.1 Key clinical features of various periodic paralyses

Clinical features	HypoKPP	HyperKPP	ATS	TPP
Age at onset	First or second decade of life	First decade of life	First or second decade	Second to fourth decade
Frequency of episodes	7 to 9 per month to sometimes several episodes per week	More frequent. Around 16 per month.	Variable	Variable
Duration of episodes	Several hours but can last up to days	Lasts shorter for around 15–60 min	Recovery within hours	Few hours to several days
Severity of episodes	Usually moderate to severe weakness but mild episodes can occur	Mild to moderate weakness	Variable	Mild to severe
Features of myotonia	Absent	Present	Absent	Absent
Trigger factors	Carbohydrate rich foods, stress, alcohol and rest after exercise	Fasting, rest after exercises and ingestion of potassium rich foods	Occurs spontaneously or rest after exercise	Carbohydrates, rest after exercise, stress, alcohol
Progressive weakness	Evolves later in course of illness	Less common	Absent	Absent

Table 24.1 (continued)

Clinical features	HypoKPP	HyperKPP	ATS	TPP
Cardiac involvement	Due to hypokalemia	Due to hyperkalemia	Prolonged QT interval and ventricular arrhythmias independent of serum potassium levels (Fig. 24.1)	Due to hypokalemia
Other features	10% of hypoKPP due with sodium channel mutations are associated with myalgia, during recovery of episodes.		Dysmorphic features: short stature, low set ears, hypertelorism, micrognathia, clinodactyly, syndactyly and high-arched palate (Fig. 24.1).	Features of thyrotoxicosis

Tawil et al. (1994), Sansone et al. (1997), Statland and Barohn (2013), Venance (2006), and Lin (2005)

24.4 Pathophysiology

Primary periodic paralyses are characterized by variable penetrance and intrafamilial variability. They are caused by mutations in genes encoding for skeletal muscle ion channels. Periodic paralyses share a common final mechanistic pathway, i.e. aberrant depolarization. This inactivates sodium channels and renders the muscle fibre unexcitable. In TPP, due to hyperadrenergic activity, there is potassium shift into the cells. Hence, beta antagonists can be used gainfully in these cases. The affected channels, genes and common mutations have been tabulated in Table 24.2.

24.5 Investigations

While investigating a patient with periodic paralysis, it is important to rule out secondary causes of episodic weakness. Among periodic paralysis, a variety of investigations that help to characterise a particular disorder are tabulated in Table 24.3.

24.6 Differential Diagnosis

It is important to differentiate between primary and secondary periodic paralyses as they much differ from management point of view. Weakness due to secondary hypokalemia can be caused by excess renal loss (hyperaldosteronism, renal tubular acidosis, etc.), gastrointestinal potassium loss (villous adenoma, non-tropical sprue)

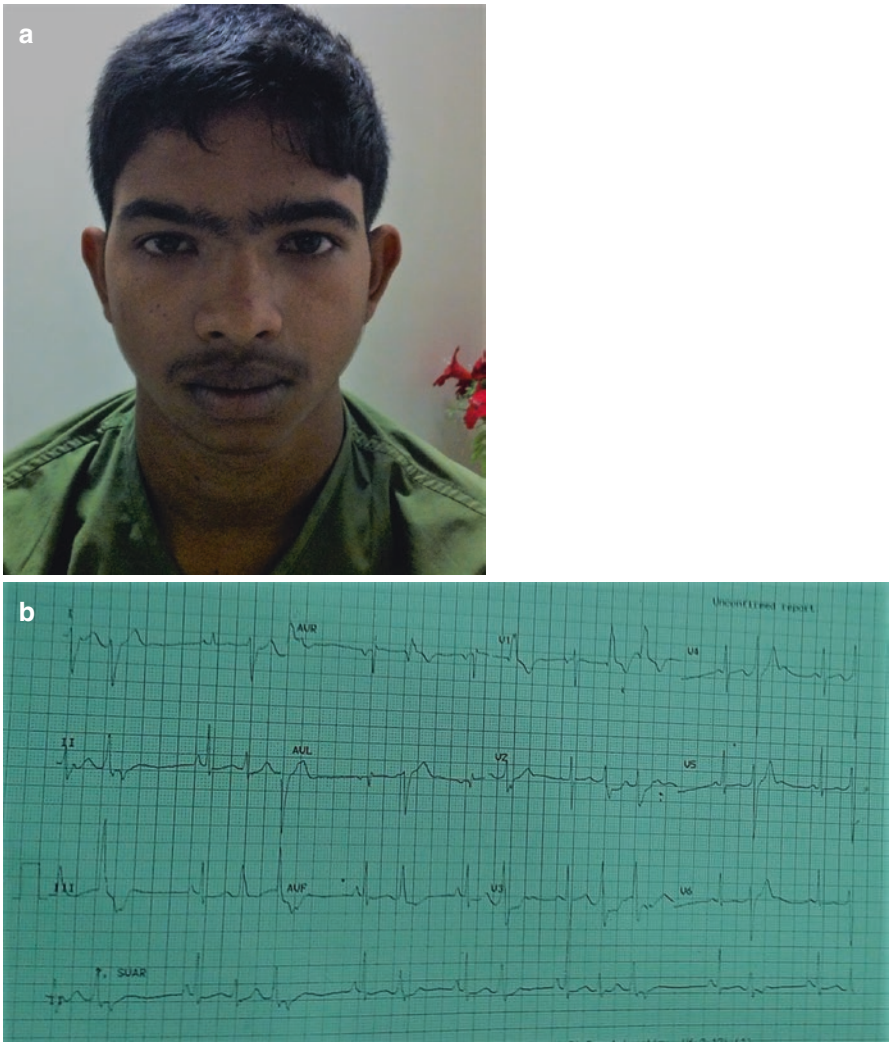

Fig. 24.1 (**a**) Dysmorphic facial features and (**b**) ventricular bigeminy in a patient with ATS

Table 24.2 Genetic mutations and ion channels dysfunction in various periodic paralyses

Diseases	Ion channels	Affected genes	Common mutations
HypoKPP 1	Calcium	CACNA1S (70–80%)	Arg-528-His and Arg-1239-his mutations in S4 segments
HypoKPP 2	Sodium	SCN4A (10–20%)	Arg-669-His and Arg-672-His
HypoKPP 3	Potassium	KCNE3 (rare)	Arg-83-His
HyperKPP	Sodium	SCN4A	T704 M and M1592 V mutations
ATS	Potassium	KCNJ2 (Kir 2.1)	Most are missense mutations
TPP	Potassium	Kir 2.6 (KCNJ 18)	Arg399X, Gln407X

Venance (2006), Thethi et al. (2014), and http://neuromuscular.wustl.edu/mtime/mepisodic.html

Table 24.3 Salient investigational findings in various periodic paralyses

Investigations	HypoKPP	HyperKPP	ATS	TPP
Ictal potassium levels	Low	Normal or high	Low, normal or high	Low
Electrocardiogram	Absent T-waves, appearance of U waves and prolonged P-R interval	Tall T-waves	Prolonged QT interval, polymorphic ventricular ectopics	Same as in hypoKPP
Compound muscle action potentials (CMAPs) after short exercise	No change (Fournier pattern V)	Increase in amplitude (Fournier pattern IV)	No change	No change
CMAP after long exercise	Late decrement	Initial increment followed by late decrement	No change	No change
Myotonic discharges	Absent	Can occur	Absent	Absent
Muscle biopsy	Vacuolar changes. In case of fixed weakness, changes of myopathy can be seen	Vacuolar changes	Tubular aggregates more commonly seen	Presence of vacuolation
Genetic testing	Refer Table 24.2			

Statland and Barohn (2013), Statland et al. (2014), Venance (2006), and Fournier et al. (2004)

and drugs (potassium depleting diuretics, corticosteroids). Renal tubular acidosis leading to secondary hypokalemic paralysis may herald the onset of Sjogren's syndrome. Close differentials with their key differentiating features are summarised in Table 24.4.

24.7 Management

Management consists of abortion of acute episode and medications to reduce frequency or severity of further attacks. As patients can have accompanying ECG changes and cardiac arrhythmias due to altered serum potassium levels, they may require continuous cardiac monitoring. Various treatment strategies during acute episodes have been summarised in Table 24.5.

It is important to appreciate that in spite of the severity of the condition, majority of patients can be managed by oral medications. In hypoKPP, oral supplementations in the doses of 0.5 to1 mEq/kg can be used successfully. About 40–60 mEq of potassium rises the serum potassium by about 1 mEq/L. Intravenous potassium is reserved for cardiac arrhythmias or respiratory failure.

Table 24.4 Differential diagnosis of periodic paralysis with their key differentiating features

Differentials of hypoKPP	Diseases	Key differentiating features
	Secondary hypokalemia	Unlike hypoKPP, facial, bulbar and respiratory muscles can be severely affected. Treatment is potassium supplementation without acetazolamide (ACTZ)
	TPP	Asian preponderance, male dominance, later age of onset, mild to severe episodes, weakness not necessarily occurring during morning hours, systemic features of thyrotoxicosis, no pattern on exercise testing and treatment are beta blockers rather than ACTZ
	Congenital myasthenic syndrome	Involvement of ocular, bulbar, facial and respiratory muscles, repetitive CMAPs can be present on nerve conduction studies, no particular triggers, normal serum potassium during weakness and treatment is pyridostigmine, aminopyridine, salbutamol or fluoxetine
	Guillain–Barré syndrome	Wide age of onset; no family history; progressive weakness evolving over days; involvement of facial, bulbar, neck and respiratory muscles; presence of autonomic dysfunction; sensory complains; raised CSF proteins; and gradual recovery over days and weeks
Differentials of hyperKPP	Refer to differential diagnosis section in chapter: nondystrophic myotonias	

Table 24.5 Various treatment strategies in periodic paralysis

Treatment strategies	HypoKPP	HyperKPP	ATS	TPP
Potassium supplementation	Yes	No	Yes	Yes
IV glucose plus insulin	No	Yes	No	No
IV calcium gluconate	No	Yes	May be required for cardiac arrhythmias	No
Beta blockers	No	No	Cardiac arrhythmias	Yes. Drug of choice
Inhaled beta agonist	No	Yes	No	To be avoided
Others	Mild exercise	Mild exercise	Mild exercise; amiodarone for cardiac arrhythmias	Control of thyrotoxicosis

Some prophylactic measures can help to reduce frequency and severity of attacks and help in reducing disability of patients (Table 24.6). Prophylactic measures for TPP and hypoKPP are similar except that there is no role of ACTZ and beta blockers are drug of choice in the former.

Table 24.6 Some prophylactic measures in periodic paralysis

Prophylactic measures	HypoKPP	HyperKPP	ATS
Diet	Low-carbohydrate and low-salt diet; avoid alcohol	Avoid fasting	If potassium low during attacks, then low-carbohydrate and low-salt diet
Oral potassium supplement	Yes	No	Yes
ACTZ (125–1000 mg per day)	Yes	Yes	Yes
Spironolactone (25-100 mg)	Yes	No	Yes
Thiazide diuretic	No	Yes	No

Statland et al. (2014), Venance (2006), Suetterlin et al. (2014), Smith et al. (2006), and Sharp and Trivedi (2014)

24.8 Prognosis

As periodic paralyses spare bulbar and respiratory muscles, they are not life threatening. But accompanying cardiac arrhythmias may pose a risk. Recurrent weakness and, sometimes, fixed proximal weakness can cause significant morbidity.

24.9 Case Study

Clinical details: A 30-year-old lady presented with acute onset flaccid quadriparesis which evolved over a period of 24 h. She had mild change in speech and dyspnoea on lying down. Weakness was associated with pain in all four limbs. There was no history of sensory complaints, fever, diarrhoea or any viral illness prior to the onset of weakness. She did not have any neuropsychiatric complaints or autonomic involvement. Bowel and bladder functions were unaffected. On examination, there was symmetrical, severe, proximal (grade 2/5) more than distal (grade 3/5) limb weakness. All deep tendon reflexes were depressed, but elicitable on reinforcement and sensory system was normal. On third day of illness, NCS was normal. As a protocol for evaluation of acute flaccid quadriparesis, ECG was done, and it showed prolongation of QT interval and appearance of U waves. Serum potassium was 2.3 mEq/L.

Summary: The 30-year-old female presented with acute flaccid quadriparesis with pain and depressed deep tendon reflexes and hypokalemia.

Discussion: Clinical possibilities of GBS and hypokalemic paralysis were considered. Hypokalemic paralysis is a common differential diagnosis of GBS. Although clinical features overlap, following points favour the possibility of hypokalemic paralysis in a patient with acute flaccid quadriparesis:

- Pain and myalgias associated with weakness
- Relatively short duration of time to reach maximum weakness

- Absence of sensory symptoms or signs
- Preserved deep tendon reflexes
- Rapid recovery
- Reversal of NCS abnormalities immediately after resolution of clinical features
- Normal CSF examination
- Normal CK levels (CK levels may be elevated in hypokalemic)

Once hypokalemic paralysis has been suspected, it is important to differentiate between the primary hypoKPP and secondary hypokalemic paralysis. The following points favour possibility of hypoKPP:

- Episodic weakness lasting usually up to few hours
- Sparing of bulbar and respiratory muscles
- Precipitation by carbohydrate rich meals, stress and exercise
- Onset in first to second decade
- Presence of similar complaints in family members

Clinical and investigational features help to differentiate between different diseases that can lead to secondary hypokalemic periodic paralysis.

- History suggestive of malabsorption (gastrointestinal loss of potassium, e.g. celiac disease)
- History of consumption of medications, e.g. diuresis and corticosteroids
- History of dry mouth, dry eyes, renal calculi and features of renal tubular acidosis (metabolic acidosis, increased urinary pH and serum chloride levels), e.g. Sjogren's syndrome
- History suggestive of thyrotoxicosis, e.g. TPP
- History of hypertension and pedal oedema, e.g. hyperaldosteronism

Our present patient had renal calculi and features of renal tubular acidosis. Retrospectively, she had dry eyes and dry mouth. Antinuclear antibody (ANA), anti-SSA and anti-SSB were strongly positive. Thus, diagnosis of Sjogren's syndrome was confirmed. Patient was treated with intravenous potassium, and her weakness improved over a period of 2 days. Hypokalemic paralysis may be the initial presentation of Sjogren's syndrome.

Key Points

When to suspect

- Brief, repetitive events of quadriparesis
- Triggers like stress, carbohydrate meals, fasting and diarrhoea
- Family history

How to diagnose

- Serum potassium levels
- Electrocardiogram
- Genetic studies

How to treat

- Avoiding trigger factors
- Potassium supplements
- Cardiac monitoring
- Genetic counselling

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Part V

Exercise Intolerance, Muscle Stiffness, Cramps and Contractures

Metabolic Myopathies

25

25.1 Introduction

The first metabolic myopathy was described in 1951, a glycogen storage disease in a young man with exercise-induced cramps, the McArdle disease. Many enzymes in the glycolytic and glycogenolytic pathway have been subsequently associated with metabolic myopathies (Fig. 25.1). Similarly, fatty acid oxidation defects affect free fatty acid transport or beta oxidation. Most patients have myopathic symptoms, but some of them, e.g. glutaric aciduria type II, predominantly present with central nervous system manifestations. The mitochondriopathies refer to metabolic genetic defects that affect the electron transport chain and lead to exercise intolerance with or without rhabdomyolysis or fixed weakness. The term mitochondrial cytopathy is preferred for patients with multisystemic clinical manifestations, and the term mitochondrial myopathy is used when skeletal muscle is the predominant tissue involved.

25.2 Epidemiology

Mode of transmission:

- Glycogen storage diseases:
  - All except phosphorylase b kinase deficiency, phosphoglycerate kinase 1 deficiency: autosomal recessive
  - Phosphorylase b kinase deficiency, phosphoglycerate kinase 1 deficiency: X-linked recessive
- Fatty acid oxidation defects: autosomal recessive
- Mitochondrial diseases: maternal transmission, autosomal dominant, autosomal recessive, X-linked

Common fatty acid oxidation defects: carnitine palmitoyl transferase II deficiency, trifunctional protein deficiency, very-long-chain acyl-CoA dehydrogenase deficiency

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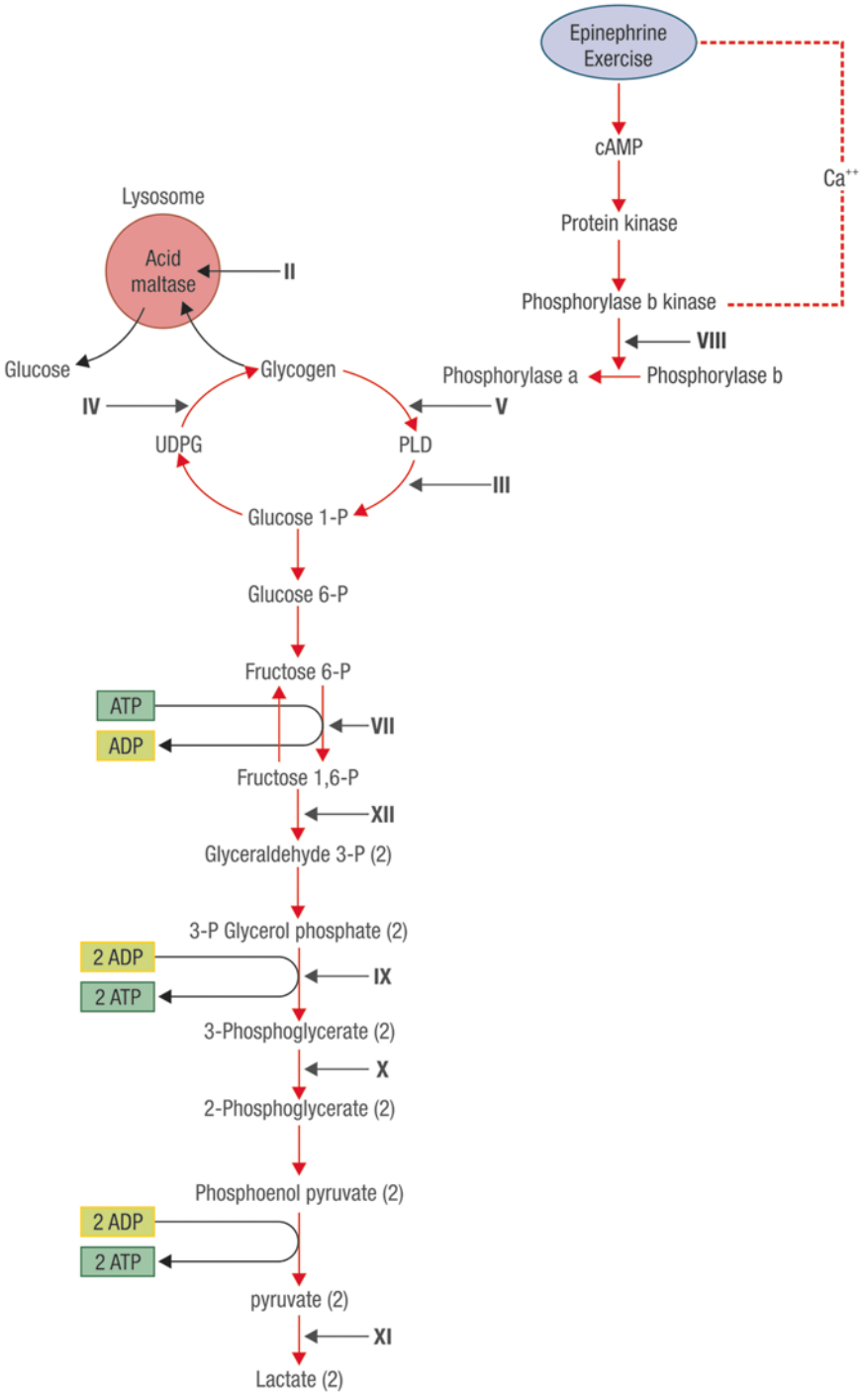

Fig. 25.1 Glycolytic and glycogenolytic pathway

25.3 Clinical Features

25.3.1 Glycogen and Lipid Storage Disease

For clinician, the following points are important to know:

- Interictal examination is normal or may show muscle weakness and systemic features.
- Type of exercise that provokes episodes.
- Triggers (Table 25.1).

Clinical presentations vary with age:

- Muscle glycogenosis:
  - Infancy: multisystem involvement (Tein 1999)
  - Adult: exercise intolerance, isolated progressive muscle weakness (Eymard and Laforêt 2001)
- Fatty acid oxidation defect:
  - Infancy or childhood: liver and/or brain involvement
  - Adult: myopathy

Table 25.1 outlines the main clinical features of both the groups in general and some important specific diseases.

Table 25.1 Clinical features of glycogen and lipid storage diseases

Glycogen storage disease	Lipid storage disease
General features	
1. Exercise intolerance with normal examination 2. Fixed weakness	
Short bursts of high-intensity exercise produce symptoms Second wind phenomenon (McArdle disease): 10 minutes of aerobic exercise causes significant improvement in exercise tolerance (Haller and Vissing 2002; Taivassalo et al. 2003; Ørngreen et al. 2008; Deschauer et al. 2005)	Prolonged exercise produces myalgias Fasting precipitates myalgias and weakness
Out-of-wind phenomenon (PFK deficiency): Muscle symptoms are worsen with glucose or sucrose intake prior to exercise (Haller and Vissing 2004)	
Haemolytic anaemia: Seen in GSD types VII, IX and XII M subunit of phosphofructokinase present in erythrocyte (Tsujino et al. 2000)	
Mental retardation or dementia: Adult polyglucosan body disease, GSD type IX and XII	
Myogenic hyperuricemia: Which can lead to many glycogen storage diseases (Mineo and Tarui 1995)	

(continued)

Table 25.1 (continued)

Glycogen storage disease	Lipid storage disease
Diseases	
McArdle disease • Most frequent genetic myopathy (Haller 2000) • Do not tolerate static or isometric muscle contractions as well dynamic exercise • Muscle cramps, fatigue, contractures and myoglobinuria • Severe elevation of serum CK • Second wind phenomenon present • Sugar intake ameliorates symptoms (Vissing and Haller 2003; Vissing et al. 2005)	CPT II deficiency • Most common • Frequent episodes of myalgias, muscle stiffness, weakness • Precipitated by prolonged fasting or exercise and infections • Myoglobinuria • Asymptomatic between attacks • Renal failure • Respiratory failure
Pompe's disease • Infantile form: Floppy baby, cardiomegaly, respiratory failure (Kishnani et al. 2006) • Juvenile form: Cardiomyopathy less common • Adult form: Fixed muscle weakness and respiratory failure	VLCAD deficiency • Infancy • Multisystem disease • Presentation could be similar to CPT II (Hamano et al. 2003)
Cori–Forbes disease: Distal muscle weakness, heart muscle involvement, hepatomegaly, polyneuropathy, hypoglycaemia (Shen et al. 1996)	MADD (glutaricaciduria type II) • Progressive muscle weakness • Later presentations known • Some patients respond to riboflavin or coenzyme Q10 supplementation (Horvath et al. 2006)

Abbreviations: *CPT*, carnitine palmitoyl transferase; *VLCAD*, very-long-chain acyl-CoA deficiency; *MADD*, multiple acyl-CoA dehydrogenation deficiency

25.3.2 Mitochondrial Diseases

Mitochondrial diseases present as either isolated muscle disease or a part of systemic disease. Exercise-related presentation is more common than fixed weakness. Exercise intolerance is out of proportion to weakness (Berardo et al. 2010). Exercise induces subjective muscle heaviness or burning sensation. Absence of stiffness, cramps or second wind phenomenon differentiate them with glycogenosis. Other differentials that need to rule out are chronic fatigue syndrome and fibromyalgia. Table 25.2 lists the key clinical features of main groups of mitochondrial myopathies.

Table 25.2 Clinical features of mitochondrial diseases

Disease	Key features
Kearns–Sayre syndrome (KSS)	Obligatory triad of: • Onset prior to 20 years of age • Extraocular muscle weakness • Pigmentary retinopathy Plus one of the following: • Ataxia • CSF protein level > 100 mg/dL • Cardiac conduction blocks
Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)	Atypical strokes • Before 40 years of age • Distribution is not in vascular territory (Sproule and Kaufmann 2008) Maternal inheritance Diabetes, hearing loss, migraine-like headaches in relatives
Myoclonus epilepsy with ragged red fibres (MERRF)	Maternally inherited disorder Clinical triad of myoclonus, epilepsy and ataxia Muscle biopsy shows ragged red fibres
Myopathic form of coenzyme Q10 deficiency	Proximal muscle weakness Early fatigue Weakness Raised creatine kinase and lactate (Gempel et al. 2007)

25.4 Pathophysiology

Glycogen, glucose and free fatty acids are important for adenosine triphosphate production in cells. Pyruvate, glycogen metabolism product, enters into the mitochondria. Carnitine transporter system allows long-chain fatty acid to enter mitochondria while short- and medium-chain fatty acids have free access. Carnitine transporter system involves acylcarnitine translocase and carnitine palmitoyl transferases I and II. After entering into the mitochondria, all these substrates are metabolised to acetyl coenzyme A, which is an important substrate for ATP production through Krebs cycle (Fig. 25.2).

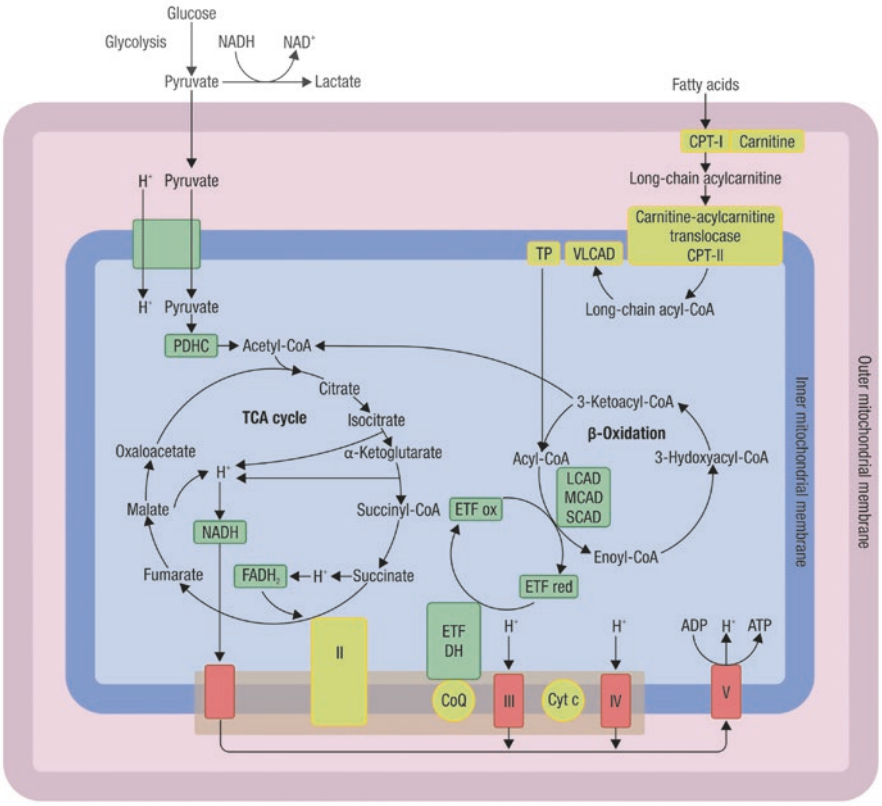

Fig. 25.2 Krebs cycle

25.5 Investigations

Table 25.3 lists the tests employed in various disease categories (Tarnopolsky 2016).

Table 25.3 Diagnostic tests

Disease	Testing
Glycogen storage disease	• Serum creatine kinase is chronically raised in the McArdle disease; otherwise, it is usually normal in the other glycogen storage diseases • Serum uric acid is elevated in approx. 50% • Forearm exercise test shows no lactate with high ammonia rise (Hanisch et al. 2006; Kazemi-Esfarjani et al. 2002; Tarnopolsky et al. 2003) • Graded exercise stress test: Second wind phenomenon is seen in the McArdle disease no second wind phenomenon suggests the glycolytic defects • EMG is often normal in cases of glycogen storage disease • Muscle biopsy may show high glycogen, absent phosphorylase or absent phosphofructokinase (Tsuburaya et al. 2012) • Genetic testing options • Specific mutation analysis: (R49X in È-70% of white individuals with the McArdle disease) • Next-generation sequencing panels for glycogen storage diseases or myopathy panels with glycogen storage disease genes or whole-exome sequencing
Fatty acid oxidation defects	• Serum CK usually normal • Serum total carnitine often normal • Serum acylcarnitine profile often abnormal (fasted or following a graded exercise stress test) • Urine organic acids (dicarboxylic acids) may be elevated • Hypoketotic hypoglycemia during an event • Skin biopsy for enzyme analysis and acylcarnitine in fibroblasts • Specific mutation analysis (S113 L in È70%) in blood • Often have normal • Muscle biopsy may show increased lipids but usually nonspecific findings
Mitochondrial myopathy	• Raised serum CK • Raised serum lactate • Serum alanine is occasionally elevated • Urine organic acids (tricarboxylic acid intermediates, 3-methylglutaconic aciduria) may be elevated • Forearm exercise test does not lead to deoxygenation • Graded exercise stress test is associated with low VO2max, high respiratory exchange ratio • EMG is often normal [used as a tool to rule out myotonic disorders and muscular dystrophies if the diagnosis is not clear] • Muscle biopsy may show ragged red fibres (Rowland et al. 1991), cytochrome oxidase negative fibres or paracrystalline inclusions (electron microscopy) • Enzyme analysis on muscle and skin fibroblasts can show mixed or single electron transport chain defects • Genetic testing options (usually on muscle tissue) • Specific mutation analysis for classic features of mitochondrial encephalomyopathy, lactic acidosis, and stroke like episodes (MELAS) (m.3243A9G) (Marotta et al. 2009); Leber hereditary optic neuropathy (m.11778G9A, m.14484T9C, m.3460G9A); chronic progressive external ophthalmoplegia (mitochondrial DNA deletion); or myoclonic epilepsy with ragged red fibres (MERRF) (m.8363G9A) (Bortot et al. 2009; Pulkes et al. 2005; Andreu et al. 1999a, b; Downham et al. 2008; McFarland et al. 2004; Wiedemann et al. 2008; Melone et al. 2004; Mehrazin et al. 2009) • Mitochondrial DNA sequencing (if mitochondrial DNA mutation is suspected) (Zeviani et al. 1998) • Next-generation sequencing targeted mitochondrial panels or whole-exome sequencing (both for nuclear mutations)

25.6 Differential Diagnosis (Table 25.4)

Differential diagnosis of metabolic myopathies have been mentioned in Table 25.4.

Table 25.4 Differential diagnosis of metabolic myopathies

Disease category	Key differentiating features
Structural myopathies • Muscular dystrophies (dysferlinopathies, anoctaminopathies, sarcoglycanopathies, etc.) • Malignant hyperthermiaSymptoms may be triggered by exercise Also called as pseudometabolic myopathies (Lahoria et al. 2014; Nguyen et al. 2007; Veerapandiyan et al. 2010)	Persistence of elevation of serum CK beyond 10 days of event of rhabdomyolysis
Statin myopathy (myalgia and exercise-induced increase of symptoms) (Wu et al. 2014; Parker et al. 2012)	Use of statins Improvement after stoppage of offending agent Statins can unmask a metabolic myopathy (fatty acid oxidation defects, glycogen storage disease and mitochondrial cytopathies) (Vladutiu et al. 2006)

25.7 Management

The general principles of management are based on avoiding the precipitating factors and using specific agents when available (Table 25.5).

Table 25.5 Specific therapies for metabolic myopathies

Disease	Recommendations
Pompe's disease	Enzyme replacement therapy: Indicated for symptomatic patients. Status unclear for asymptomatic and advanced cases. Point of discontinuation also debated (Cupler et al. 2012; Kishnani et al. 2012, Orlikowski et al. 2011)
Cori disease	Frequent meals, high carbohydrate and high protein intake, raw cornstarch (Kishnani et al. 2010)
McArdle disease	Aerobic training, prolonged treatment with vitamin B6 (Haller et al. 1983; Sato et al. 2012), physical training and dietary supplements (Quinlivan et al. 2014, 2011), sucrose infusions before exercise (Andersen et al. 2008), carbohydrate-rich diet (Andersen and Vissing 2008) and moderate aerobic exercise program (Lucia et al. 2013). Ramipril (Martinuzzi et al. 2003, 2008), low-dose creatine monohydrate (Vorgerd et al. 2000) and pre-exercise fructose (Preisler et al. 2015)
Fatty acid oxidation disorders (mainly CPT II)	High carbohydrate foods before exercise improve endurance (Ørngreen et al. 2002, 2003), administration of vitamin B2 (riboflavin), medium-chain triglyceride oil and L-carnitine (Longo et al. 2006), bezafibrate suggested but role not clear (Ørngreen et al. 2014) and triheptanoin (odd chain free fatty acids) shown to improve exercise capacity (Vockley et al. 2015)

Table 25.5 (continued)

Disease	Recommendations	
Mitochondrial disorders	Bypass specific electron transport chain • Succinate and riboflavin • Coenzyme Q10 • Antioxidants: Vitamins E and C, alpha lipoic acid, idebenone and coenzyme Q10 • Creatine monohydrate • Combined approach: Mitochondrial cocktail (Rodriguez et al. 2007)	
Drugs for mitochondrial myopathies	Dose	Side effects
Co Q 10	30 mg three times a day	Nausea, diarrhoea, upset stomach or appetite loss
Vitamin C	500 mg twice a day	
L-carnitine	500 mg twice a day	
Creatine monohydrate	2.5 g twice a day	Occasional mild stomach upset
Thiamine and riboflavin	100 mg once a day	Riboflavin causes urine to turn bright yellow
Alpha lipoic acid	200 mg three times a day	Mild stomach upset, allergic skin reaction
Arginine	500 mg twice a day	

25.8 Prognosis

Lifestyle and dietary modifications are known to improve the quality of life of patients with metabolic myopathies. In some individuals, progressive muscular weakness and resultant disabilities accumulate with time. Patients with mitochondrial myopathies should be evaluated annually for known complications like cardiac and diabetes (Parikh et al. 2015).

25.9 Case Study

Clinical features: A 32-year-old male was admitted to the intensive care unit with history of acute onset of breathlessness. He had developed easy fatigability and reduced exercise tolerance since 1 year before presentation. He has also noticed difficulty in getting up from sitting position and performing overhead activities due to proximal muscle weakness. The patient was born of nonconsanguineous marriage, and there was no history of similar illness in family. There was no history of fluctuations, fatigability, diplopia, ptosis, bulbar weakness or dark-coloured urine. On examination, the patient was breathless and needed invasive ventilatory support due to poor respiratory efforts. There was symmetrical proximal (lower limbs 3/5; upper limbs 4/5) muscle weakness. Respiratory muscle weakness, out of proportion to limb weakness, was very striking.

Summary: A 32-year-old male presenting with gradually progressive, respiratory and proximal muscle weakness without any fluctuations, fatigability or bulbar weakness.

Discussion: CK levels were 750 IU and NEE confirmed myopathy. Breathlessness in myopathic illness occur secondary to cardiac involvement or respiratory muscle weakness or both. Respiratory muscle weakness eventually occurs at advanced stage of many muscle diseases. However, respiratory muscle weakness can be early and prominent in some muscle diseases:

- Late-onset Pompe's disease
- Nemaline myopathy
- Fukutin-related proteinopathy
- Inflammatory myopathy
- Myotonic dystrophy
- Desminopathy
- Mitochondrial myopathy

Cardiac involvement can present as cardiomyopathy (e.g. infantile Pompe's disease, myotilinopathy, laminopathy, sarcoglycanopathy, Duchenne muscular dystrophy, desminopathy and carnitine deficiency) or cardiac arrhythmias (Emery–Dreifuss muscular dystrophy, myotonic dystrophy, Kearns–Sayre syndrome and laminopathy).

ECG and 2D Echo were normal in our patient. Muscle biopsy showed characteristic glycogen laden muscle fibres, suggestive of glycogen storage disease (Fig. 25.3). Alpha-glucosidase levels were 0.1 nmoles/hour/mg (normal value is 56–296). Final diagnosis of adult-onset Pompe's disease was made. Patient improved with myozyme and supportive care. It is important for clinicians to appreciate that:

- Acid maltase deficiency can present in adults.
- Adults tend to have lesser systemic features like hepatosplenomegaly.
- It should be suspected in patients with limb girdle weakness and prominent breathlessness.
- Presentation can be with fixed weakness.
- Light microscopy with haematoxylin and eosin and PAS stain can pick up glycogen-laden fibres.

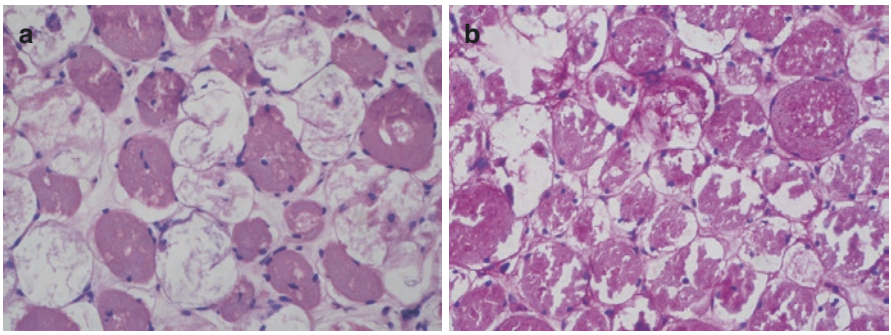

Fig. 25.3 (**a**) Haematoxylin and eosin stain show large vacuoles in many muscle fibres, and (**b**) PAS stain shows PAS positive material (glycogen) in many of these cells in a patient with adult-onset Pompe's disease (Courtesy: Department of Pathology, Bombay Hospital, Mumbai)

This is a rare, progressive but a treatable cause of myopathy.

Salient clinical and investigational features that can help to differentiate amongst different forms of metabolic myopathies are summarised in Table 25.6.

Table 25.6 Salient clinical and investigational features of some metabolic myopathies

Exercise intolerance	Key features of different metabolic myopathies
High intensity <10 min associated with cramps, myalgias and exercise-induced myoglobinuria	PPL (McArdle, type V) – presence of second wind phenomenon; raised ammonia and CK levels on exercise but normal lactate levels; PPL deficiency can be demonstrated on muscle biopsy by biochemistry, IHC or both; PYGM gene mutations to confirm diagnosis PFK (Tarui, type VII) – absence of second wind phenomenon; worsening of symptoms with carbohydrates; presence of haemolytic anaemia; PFK deficiency detected on muscle biopsy PGK (type IX) isoform A – absence of second wind phenomenon; worsening of symptoms with carbohydrates; haemolytic anaemia can occur; presence of proximal weakness and mental retardation; PGK deficiency detected on muscle biopsy. PGAM (type X) – absence of second wind phenomenon; no worsening of symptoms with carbohydrates; PGAM deficiency on muscle biopsy
Low intensity >10 min associated with muscle pain, transient weakness and recurrent myoglobinuria	CPT II deficiency – baseline normal CK; muscle biopsy is usually normal; CPT gene mutations are diagnostic VLCAD deficiency – baseline normal CK; increased serum long-chain acylcarnitines; normal/low free carnitine; VLCAD deficiency on cultured fibroblasts TFP – increased serum long-chain 3-hydroxy-acylcarnitines; dicarboxylic acidurias and beta-oxidation defects on cultured fibroblasts
Proximal weakness	Mitochondrial disease – it can present either with isolated muscle weakness or as a multisystem disorder; presence of red ragged fibres on muscle biopsy; muscle mitochondrial DNA testing and assessment of biochemical activities of respiratory chain enzymes can help in diagnosis

Key Points

When to suspect

- Cramps, myalgias and exercise intolerance
- Rhabdomyolysis

How to investigate

- Ischemic exercise test
- Muscle biopsy
- Genetic tests

How to treat

- Avoid trigger
- Supplementations, e.g. myozyme and mitochondrial cocktails

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Peripheral Nerve Hyperexcitability Syndromes

26

26.1 Introduction

PNH syndromes are caused by spontaneous discharges originating from the motor fibres, which lead to increased activity of the muscles. The term is broadly interchangeable with cramp-fasciculation syndrome (CFS), myokymia, neuromyotonia (NMT), Isaacs' syndrome and Morvan's syndrome. Antibodies directed against voltage-gated potassium channels (VGKC) located in the terminal segments of the peripheral nerves seem to be pathogenic for many of these diseases. A proportion of patients experience sensory nerve involvement and autonomic dysfunction, e.g. hyperhidrosis, and develop central nervous system (CNS) features such as mood changes, sleep disorders and hallucinations. Immune-mediated PNH can be associated with other autoimmune diseases and also occur as a part of paraneoplastic syndrome secondary to malignancies. Some features of PNH can be seen secondary to peripheral neuropathy and degeneration of anterior horn cells. A small subgroup of PNH is known to be genetic in origin and hence familial. It is important for clinicians to recognise PNH, as these patients can require long-term immunosuppression and screening for underlying tumours (Skeie 2010; Hart et al. 2002; Küçükali et al. 2015; Maddison 2006). Based on aetiology, PNH syndromes can be classified into following subtypes as mentioned in Table 26.1.

26.2 Epidemiology

The syndrome of continuous muscle fibre activity was first described by Isaac in 1961. In 1965, Mertens and Zschocke described the term 'neuromyotonia' (NMT). In 1993, Newsom–Davis and Mills described the immunological associations of NMT. Morvan described a syndrome similar to that observed by Isaac, but these patients had additional features of encephalopathy. He used the term 'fibrillary chorea', but due to electrophysiological evidence of spontaneous discharges, this terminology became unpopular (Gutmann and Gutmann 2004). Overall, PNH syndromes

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Table 26.1 Etiological classification of PNH syndromes

PNH primary, immune mediated (often VGKC) or paraneoplastic	*Primary/idiopathic*: CFS, Isaacs' syndrome and Morvan's syndrome *Associated with other autoimmune disorders*: MG, SLE, CIDP, autoimmune thyroid disease and rheumatoid arthritis *Paraneoplastic syndromes*: Thymoma, small-cell lung carcinoma, lymphoma and other haematological malignancies [Note: Satoyoshi syndrome is an idiopathic autoimmune disorder that can be included in PNH spectrum]
Secondary PNH – PNH is associated with changes of denervation	*Peripheral neuropathy*: CIDP, GBS, entrapment neuropathy like CTS, radiation plexopathies/neuropathies, radiculopathy *Anterior horn cell degeneration*: ALS, SMA *Toxins*: gold, alcohol, snake venom, insecticide [Note: facial myokymia can occur secondary to brainstem neoplasm or demyelination]
Genetic and hereditary diseases	VGKC (KCNA1) mutations Familial episodic ataxia 1(EA1) Hereditary neuropathy (HINT1 mutation) Schwartz–Jampel syndrome (SJS)

MG, myasthenia gravis; *SLE*, systemic lupus erythematosus; *CIDP*, chronic inflammatory demyelinating neuropathy; *GBS*, Guillain–Barré syndrome; *ALS*, amyotrophic lateral sclerosis; *SMA*, spinal muscular atrophy; *HINT1*, histidine triad nucleotide-binding protein

are more common in males than females, with peak onset in fourth or fifth decade of life (Hart et al. 2002; Rubio-Agusti et al. 2011). In a case series of 29 patients with Morvan's syndrome, 27 of these patients were male (Irani et al. 2012). The cause of this male preponderance is still unknown. In a case series of 38 patients with symptoms of PNH, close to 50% of patients had evidence of underlying axonal denervation without presence of VGKC antibodies. In 20% of patients with VGKC antibody positive PNH, there was presence of underlying tumour (Rubio-Agusti et al. 2011; Vernino and Lennon 2002). Pangariya et al. from Jaipur, India, described 20 clinical details of patients having neuromyotonia. They observed strong male preponderance and history of ingestion of Ayurvedic medications and commented upon the limited benefit with phenytoin but remarkable improvement after methyl prednisolone (Panagariya et al. 2006).

26.3 Clinical Features

The main clinical features of PNH are muscle twitching (fasciculations, myokymia), painful cramps and muscle stiffness (pseudomyotonia, pseudotetany) which lead to muscle hypertrophy in long-standing cases. Rarely, it can lead to muscle weakness. Other features of PNH are sensory phenomena, autonomic dysfunction and CNS involvement. Clinical features of PNH are summarised in Table 26.2.

Table 26.2 Clinical features of PNH

Muscle twitching – it is the most common symptom of PNH	*Myokymia*: It is derived from Greek word, i.e. 'kyma', meaning wave. It is a continuous, undulating, wave-like rippling of muscles, similar to a bag of worms under the skin. The ripple goes across the breadth of the muscles. It is commonly seen in lower limb muscles but can be seen in upper limbs, trunk and over face including the tongue *Fasciculations*: These are randomly occurring spontaneous single muscle twitches and lack rhythmic quality. Fasciculations are twitching along the length of muscle fibres. Fasciculations occur in CFS, which is a milder disorder in PNH spectrum
Painful cramps	Muscle cramps are painful and may be the initial symptom. These are associated with muscle spasms which are worsened on attempting muscle action. Muscle cramps often aggravate on exposure to cold
Muscle stiffness	Muscle stiffness is associated with cramps. Due to stiffness, patients develop difficulty in walking and lose their dexterity. Muscle stiffness can present in various forms as follows: *Pseudomyotonia*: Patients have delayed relaxation of muscles after voluntary contraction, e.g. slow release after a hand grip or prolonged eye closure. Unlike myotonic dystrophy, there is absence of percussion myotonia *Pseudotetany or pseudodystonia*: Spontaneous or evoked carpopedal spasm like posturing of both hands. But calcium and magnesium levels remain normal
Muscle hypertrophy	It is the result of continuous muscle activity. Most often calf muscles are hypertrophied but hypertrophy can be seen in forearm and hand muscles too. The degree of hypertrophy relates to the severity of muscle overactivity
Muscle weakness	Rarely, muscular weakness can occur due to fatigue as a result of continuous muscle fibre activity. In a rare instance, Morvan's syndrome presenting as quadriparesis has been reported
Sensory complaints	Due to sensory hyperexcitability, a proportion of patients develop paresthesias, dysesthesias and numbness
Autonomic dysfunction	Hyperhidrosis is the most prevalent and persistent manifestation of autonomic dysfunction. Other features are tachycardia, hypotension, urinary complains, constipation, hypersalivation and lacrimation
CNS involvement	CNS involvement manifests commonly as insomnia. Neuropsychiatric features such as hallucinations, confusion, delusions, agitation and amnesia occurs in most of these patients. Few patients can develop facio-brachial dystonic seizures or generalised tonic–clonic seizures

Lotan et al. (2016); Maddison (2002); Irani et al. (2012); Liewluck et al. (2014); Gutmann and Gutmann (2004); Hart et al. (2002); Abou-Zeid et al. (2012)

Clinical spectrum of PNH syndromes is wide, and CFS represents milder severity, while Morvan's and Isaacs' syndrome are severe manifestations of PNH.

- CFS: Muscle twitches and cramps ± VGKC antibody positive
- Neuromyotonia: Muscle twitching and myokymia on examination + muscle stiffness + electrophysiological evidence of myokymia or neuromyotonia
- Isaacs' syndrome: Features of neuromyotonia + hyperhidrosis ± VGKC antibody positive
- Morvan's syndrome: Features of neuromyotonia + hyperhidrosis + CNS involvement ± VGKC antibody positive

26.4 Pathophysiology

In most cases of immune-mediated PNH syndromes, autoimmune mechanisms are responsible for the disease manifestations, as they disturb the function of VGKCs. VGKCs are abundantly expressed at the cell body membrane, axons and nerve terminals of both central and peripheral nervous system neurons. These channels are known to significantly contribute to repolarisation and maintenance of the resting membrane potential. Inhibition of neuronal potassium channels by antibodies, toxins or genetic mutations leads to increased membrane excitability and spontaneous action potential discharges. Two proteins are complexed with potassium channels on the neuronal membrane: contactin-associated protein 2 (CASPR2), which is localised at the juxtaparanodes of myelinated axons, and leucine-rich glioma inactivated 1 (LGI1), which is strongly expressed in the hippocampus. Antibodies from patients predominantly react with CASPR2. Thus, CASPR2 antibody is more frequently associated with neuromyotonia or Morvan's syndrome, and LGI1 antibody is more commonly detected in patients with limbic encephalitis. However, both antibodies together or individually, can be detected in neuromyotonia, Morvan's syndrome and limbic encephalitis in varying frequencies. These antibodies are predominantly non complement fixating and produce functional neuronal dysfunction. Clinical syndromes caused by these antibodies respond favourably to immunosuppression (Küçükali et al. 2015).

26.5 Investigations

Patients with suspected PNH should undergo workup to confirm the diagnosis, detect diseases that can be associated with PNH (malignancies, immune disorder) and exclude secondary causes of PNH. The following investigations are helpful in patients with PNH (Table 26.3).

Table 26.3 Salient investigational findings in PNH

Nerve conduction studies (NCS)	Various parameters of motor and sensory NCS such as amplitude, velocity and latencies remain normal in PNH
Needle electrode examination (NEE) findings	On NEE, there is presence of spontaneous discharges such as fasciculation potentials in CFS. Myokymic discharges occurring in doublets or triplets with intraburst frequency >100 Hz and trains of successive neuromyotonic discharges up to 300 Hz can be seen in Isaacs' and Morvan's syndrome. These abnormalities were detected more in distal than in proximal muscles. NEE usually does not show any changes of denervation on voluntary activity. Presence of denervation in patients with suspected PNH should raise suspicion of secondary PNH
Serum investigations	Hyponatraemia is seen in VGKC antibody syndromes (particularly LGI1). Serum creatine kinase (CK) levels remain normal or are mildly elevated
Antibody testing	VGKC antibody is found in most patients with Morvan's syndrome, up to 50% in Isaacs' syndrome and 24% in CFS. CASPR2 is an antibody that is more frequently found than LGI1 antibody in patients with PNH. Patients should undergo testing for antibodies such as AchR, ANA, anti-GAD, RF and anti-Ro and anti-La
Cerebrospinal fluid (CSF) examination	Up to 50% patients with Morvan's syndrome have normal CSF examination. CSF examination in some patients may show raised proteins, lymphocytosis and nonspecific presence of oligoclonal bands
Electroencephalography (EEG)	EEG may show generalised slowing of the background activity and focal epileptiform discharges in a small proportion of patients with Morvan's syndrome
Magnetic resonance imaging (MRI)	MRI brain is normal in more than 90% of the patients with Morvan's syndrome. Rarely, bilateral hippocampal and frontal lobe hyperintensity can be seen
Positron emission tomography (PET)	PET scan may show focal or generalised cerebral hypometabolism. Whole body PET scan can help to detect occult tumours such as thymoma, small-cell lung carcinoma, etc.

GAD, glutamic acid decarboxylase; *AchR*, anticholinesterase receptor; *ANA*, antinuclear antibody; *RF*, rheumatoid factor
Hart et al. (2002); Maddison (2006); Irani et al. (2012); Abou-Zeid et al. (2012); Ahmed and Simmons (2015)

26.6 Differential Diagnosis

Muscle stiffness and twitching can occur in a number of diseases and need to be excluded while considering the diagnosis of PNH. Differential diagnoses with their key distinguishing features are mentioned in Table 26.4.

Table 26.4 Differential diagnosis of PNH with their key distinguishing features

Differential diagnosis	Key distinguishing features
Stiff person syndrome presents with muscle stiffness	Axial >> appendicular stiffness, extensor spasms aggravated by external stimuli such as sound, hyperlordosis, absence of muscle twitching, hyperhidrosis and autonomic dysfunction and continuous firing of normal muscle action potentials simultaneously in agonist and antagonist group of muscles favour stiff person syndrome
Tetany – patients have muscle cramps and carpopedal spasm	Presence of myokymia clinically and electrophysiologically, delayed relaxation of muscles after forceful contraction, hyperhidrosis, autonomic features and absence of perioral paresthesias favour PNH
Myotonia congenita presents as muscle hypertrophy and stiffness	A proportion of patients with PNH have delayed relaxation after forceful contraction, i.e. action myotonia. But there is absence of percussion myotonia. This phenomenon is known as pseudomyotonia. These symptoms of PNH respond almost completely with antiepileptic drugs
Schwartz–Jampel syndrome (SJS) causes muscle stiffness	Early onset, action and percussion myotonia, skeletal deformity, blepharophimosis, absence of myokymia, hyperhidrosis and presence of myotonic discharges suggest SJS
Rippling muscle disease	Rippling movements of muscles at rest, on stretching and on percussion, absence of spontaneous activity on NEE and presence of muscle weakness favour rippling muscle disease
Limbic encephalitis (LG1 antibody mediated)	Presence of facio-brachial dystonic seizures, cognitive impairment, commonly affecting elderly male, higher association with small-cell lung carcinoma and smoking favour LG1 antibody-mediated encephalitis. Coexistence of autoimmune disorders like MG and PNH is less common in LG1-mediated limbic encephalitis
EA1 – presents as muscle stiffness and myokymia on NEE	Early onset, positive family history, episodes of cerebellar ataxia and muscle stiffness lasting for seconds to minutes precipitated by stress and sudden movements, occasionally tinnitus and response to acetazolamide favour EA1
Paroxysmal neuromyotonia	It is an inherited disorder characterised by episodic neuromyotonia, stiffness and hyperhidrosis. These episodes last for few hours and are accompanied by elevated CK levels. It is a channelopathy caused by mutation of Kv1.1 subunit of KCNA1 channel. Anti-VGKC antibodies are absent

Pulkes et al. (2012); Falace et al. (2007); Jen (2007); Ahmed and Simmons (2015)

26.7 Management

Management of PNH depends on the severity and coexistence of tumours and autoimmune disorders. Hence, treatment has to be individualised to the requirements of patients. Therapy consists of symptomatic treatment with membrane stabilising agents, immunotherapy and treatment of coexisting tumours and autoimmune disorders.

26.7.1 Symptomatic Treatment

Antiepileptic medications like phenytoin, carbamazepine, sodium valproate, gabapentin, duloxetine and lamotrigine have been used for control of pain, sensory symptoms, muscle twitches and stiffness that occur in PNH. While most of patients

with milder PNH like CFS can be managed only with symptomatic treatment, these are along immunotherapy in patients with Morvan's and Isaacs' syndrome. As some of these medications can cause sedation, dizziness and hyponatraemia, choice amongst these agents should be made carefully, and doses have to be titrated slowly (Hurst and Hobson-Webb 2016; Skeie 2010).

26.7.2 Immunotherapy

Most of the patients respond favourably to following immunotherapies: plasma exchanges (PE), intravenous immunoglobulin (IVIg) and corticosteroids (CS). Cyclophosphamide and rituximab can be helpful in selected cases refractory to above treatment modalities. These observations are based on case reports or small case series, and hence information on long-term immunosuppression is very less. Relapses can be treatment with rescue therapy like PE or IVIg (Abou-Zeid et al. 2012; Hurst and Hobson-Webb 2016; Skeie 2010).

26.7.3 Aetiological Treatment

When a tumour is detected, treatment of it is known to change the course of PNH favourably.

26.8 Prognosis

CFS and Isaacs' syndrome are relatively milder illnesses and prognosis is usually good. Severe form of PNH with autonomic involvement like in Morvan's syndrome can be life threatening. Few case reports of mortality secondary to cardiac failure and arrhythmias have been reported in patients with Morvan's syndrome. Severe forms of PNH may require administration of long-term immunosuppression and compromise the quality of life.

26.9 Satoyoshi Syndrome

Satoyoshi syndrome is a sporadic autoimmune disorder predominantly affecting young Asian females. It is an extremely rare disorder and around 50 cases have been reported worldwide. It is characterised by triad of alopecia, diarrhoea and muscle cramps. Age at onset is around 6–15 years but the condition can occur in elderly population. Patients have severe progressive, intermittent and painful spasms affecting limb muscles and, sometimes, jaw muscles. Endocrine disturbances like amenorrhoea, hypoplastic uterus and alopecia can occur. Bony deformities like genu valgus/varus, lumbar lordosis, pes planus and bony fragmentations at tendon insertions can occur in early-onset cases. It is believed to be of autoimmune in origin, as Satoyoshi syndrome is associated with antibodies like ANA, anti-GAD and RF, associated with autoimmune disorders like MG and Hashimoto's thyroiditis and has a relapsing

course. Treatment of choice is immunosuppression with steroids and IVIg which may have to be used for prolonged periods of time (Matsuura et al. 2007; Ashalatha et al. 2004; Aghoram et al. 2016; Ikeda et al. 1998). Membrane stabilisers like carbamazepine and phenytoin can result in symptomatic improvements.

26.10 Ocular Neuromyotonia

Ocular neuromyotonia is an ocular motility disorder characterised by involuntary contractions of one or several ocular muscles. It affects superior oblique and lateral rectus muscles, but other muscles like inferior rectus or superior rectus can also be affected. The clinical hallmark is paroxysms of diplopia and strabismus that develop spontaneously and after holding eccentric gaze. This is a result of tonic contraction or spasm of ocular muscles. It is assumed that pulsatile compression of one of the ocular nerves by an artery results in segmental demyelination and subsequent ephaptic axonal transmission. Ocular neuromyotonia, vestibular paroxysmia and hemifacial spasm probably belong to same group of disorders. The term 'neuromyotonia' in this instance is probably misleading as this disease has a different mechanism and is not associated with VGKC antibodies. Treatment of choice is carbamazepine, phenytoin and gabapentin (Koop and Gräf 2006; Roper-Hall et al. 2013; Strupp et al. 2016).

26.11 Case Study

Clinical details: A 28-year-old man presented with complaints of intermittent stiffness of all four limbs since the last 8 years. Stiffness used to worsen in cold weather to such an extent that he had difficulty in activities of daily living like being unable to open a closed fist, walking became slow and he started taking a long time to get up from sitting position. His relatives also noticed that he became very rigid and appeared stiff in cold weather. Stiffness used to relieve with exercise and he would be better in the summer season. There was no weakness in upper or lower limbs. Considering possibility of myotonic disorder, the patient had been started on phenytoin and acetazolamide by his physician. He had remarkable improvement with these medications. One month before presentation, he had subacute onset and progressive pain in all four limbs; twitching of muscles over arms, calves and thighs; visual hallucinations; behavioural changes; insomnia; and profuse generalised sweating. On examination, he had severe grip myotonia and tonic posturing of both hands, and all muscles were hypertrophied and prominent (Fig. 26.1). Strikingly, there was no myotonia on percussion of the hypothenar muscles or forearm extensors. There were spontaneous, involuntary, undulating and vermicular movements over arms, thigh muscles and calves, which were suggestive of myokymia.

NEE showed bursts of doublets and triplets with intraburst frequency up to 40–100 Hz, thus confirming the presence of myokymic discharges (Fig. 26.2).

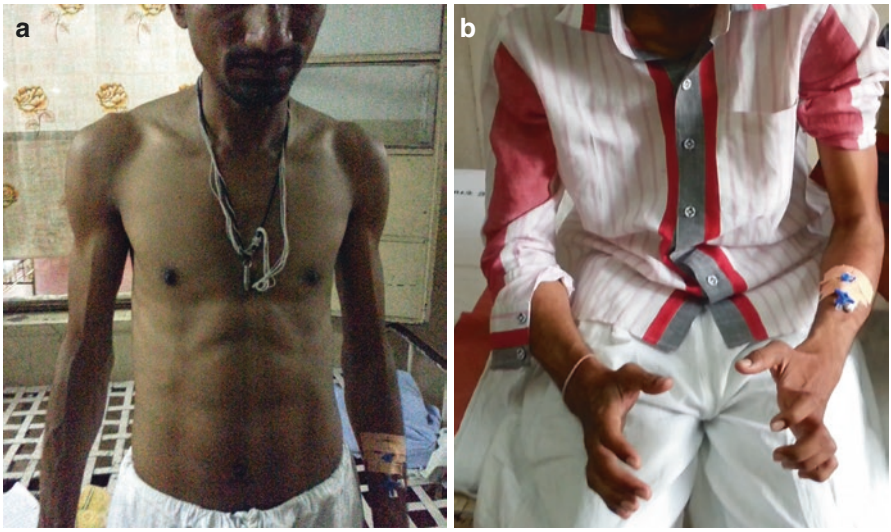

Fig. 26.1 (**a**) Muscle hypertrophy and (**b**) tonic posturing in a patient with neuromyotonia

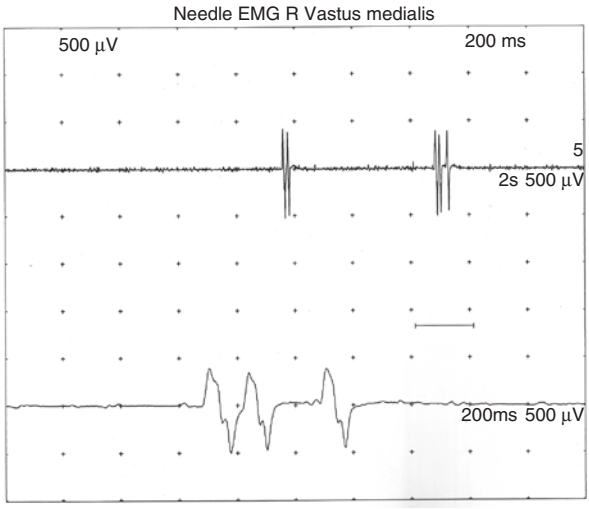

Fig. 26.2 Spontaneous activity in form of bursts of doublets and triplets

Motor and sensory NCS, CK, electrocardiogram and serum electrolytes were normal. To evaluate CNS involvement, MRI brain, CSF and EEG were done. Both these investigations were normal.

Summary: The young male presented with clinical and electrophysiological evidence of myokymia, neuropsychiatric features and autonomic dysfunction in the form of hyperhidrosis on background history of myotonia-like symptoms since 8 years and showed a complete response to phenytoin.

Discussion: It can be difficult to differentiate between PNH 'pseudomyotonia' and myotonia. The following points can help to differentiate between pseudomyotonia and true myotonia (Table 26.5).

Table 26.5 Difference between myotonia and pseudomyotonia

Pseudomyotonia	True myotonia
Patients have action myotonia, e.g. finger grip myotonia, but percussion myotonia is absent	Patients have myotonia on both action and percussion
There is complete resolution of symptoms to anticonvulsants	At best, there is partial response to anticonvulsants
NEE shows myokymia and neuromyotonic discharges	NEE shows myotonic discharges
It occurs in PNH	It occurs in dystrophic and non-ystrophic myotonias
Pseudotetany: Fixed posturing	Not seen

Key Points

When to suspect

- Muscle twitching, cramps and stiffness
- Excessive sweating
- Behavioural changes

How to investigate

- NEE showing spontaneous discharges
- VGKC antibodies
- Tumours like thymoma

How to treat

- Membrane stabilisers
- Immunomodulation
- Tumour removal

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Nondystrophic Myotonic Disorders 27

27.1 Introduction

Nondystrophic myotonias are heterogeneous group of disorders characterised by myotonia without any or minimal muscular weakness and no other systemic organ involvement. Most of the nondystrophic myotonias are caused by mutations in chloride and sodium channels. In this group, myotonia congenita (MC) forms the bulk, while paramyotonia congenita (PMC), hyperkalaemic periodic paralysis, Schwartz–Jampel syndrome (SJS), potassium-aggravated myotonias (KAM), myotonia levior and Brody syndrome are encountered in few patients. Apart from clinical and electrophysiological features of myotonia, short exercise test may show significant decrementing response. Genetic tests are available to support the diagnosis. Unlike myotonic dystrophy, these diseases are not life-threatening in general and bear excellent prognosis. Disability can be reduced by modifying triggers and using appropriate pharmacotherapy (Heatwole et al. 2013; Mankodi 2008; Statland and Barohn 2013; Ryan et al. 2007 and http://neuromuscular.wustl.edu/mother/activity.html).

27.2 Myotonia Congenita (MC)

27.2.1 Epidemiology

MC is a rare neuromuscular disease and MC has two subtypes: Thomsen's disease and Becker's disease. Thomsen's MC was first described in 1870s by a Danish physician, Thomsen, who observed myotonia in himself and his family members, which improved after repetition of movements. He also noticed that even in a family, severity of disease varies and, in subsequent studies, phenotypic variability within a family became clear. In 1977, Becker, a German neurologist, proved existence of a recessive myotonic disorder (Colding-Jørgensen 2005). It was debatable whether MC and PMC or myotonic dystrophy was a separate entity or not. But soon, Bryant

S.V. Khadilkar et al., *Neuromuscular Disorders*,
https://doi.org/10.1007/978-981-10-5361-0_27

and co-workers confirmed that Thomsen's and Becker's disease were caused by mutations in chloride channel gene CLCN 1 (Bryant and Morales-Aguilera 1971). Isolated case studies and small families of MC have been reported from India (Sinha et al. 2011; Gupta et al. 2009; Savitha et al. 2006a, b; Bhattacharyya et al. 2004).

27.2.2 Clinical Features

Typically MC presents in the first to second decade of life with features of myotonia which improves with exercise, the 'warm-up phenomenon' and a muscular build 'Herculean appearance' (Statland and Barohn 2013; Colding-Jørgensen 2005; Sinha et al. 2011) (Fig. 27.1). There is no sex predilection but men are more severely affected than women (Statland and Barohn 2013). There are two types of MC: Becker's disease which is autosomal recessive in inheritance and more common than Thomsen's disease which is transmitted as dominant trait. Details of clinical features of both forms of MC have been described below:

Thomsen's MC: Patients experience painless stiffness in infancy or childhood (Mankodi A). The upper limbs and face are predominantly affected as compared to the lower limbs. When the myotonia affects back muscles, patients have difficulty in getting up from the supine position. Muscle stiffness is worsened after period of inactivity, cold exposure or emotional surprises. These patients do not develop muscle weakness, but some develop flexion contractures at the elbow and ankle due to imbalance between forces across joints (Heatwole and Moxley 2007). Due to persistent contraction of muscles, true hypertrophy is seen in affected muscles, and

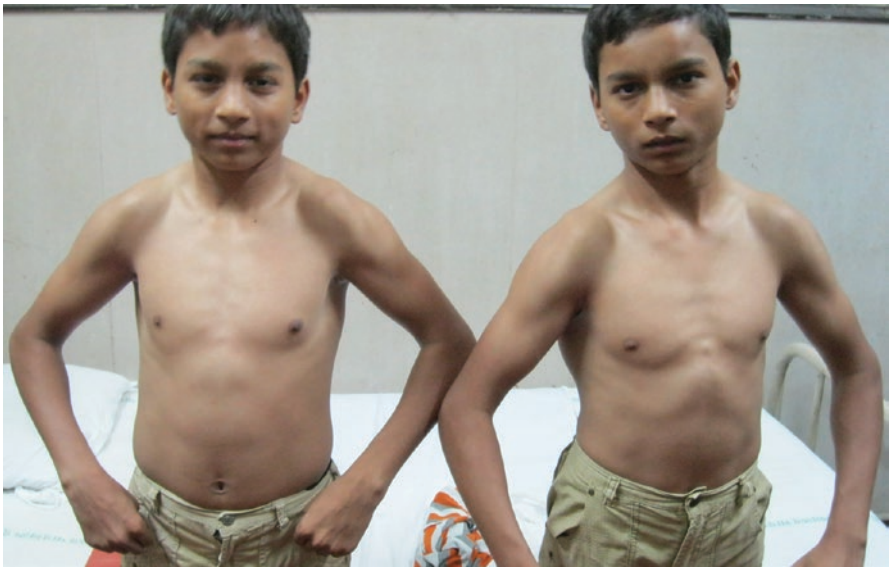

Fig. 27.1 Herculean appearance in two brothers with MC

Table 27.1 Differentiation between Becker's MC and Thomsen's MC

Features	Becker's MC	Thomsen's MC
Inheritance	Autosomal recessive	Autosomal dominant
Age of onset	Later in childhood	Infancy or early childhood
Onset of symptoms	Lower limb	Upper limb and face
Weakness	Transient weakness after prolonged rest and, sometimes, progressive weakness	Absent
Muscle hypertrophy	More pronounced	Less pronounced
Severity	More	Less
Muscle atrophy	Occasional atrophy of distal muscles	Absent

Heatwole and Moxley (2007) and Mankodi (2008)

patients appear very muscular. Myotonia can be demonstrated in many muscles but is best observed in the face and upper limbs on action (eye closure and finger grip) and on percussion of muscles (thenar eminence and wrist extensors). Fluctuating MC is a variant of Thomsen's disease, in which muscle hypertrophy is not prominent (Heatwole and Moxley 2007; Statland and Barohn 2013; Mankodi 2008; Ryan et al. 2007).

Becker's MC: Clinical appearance of myotonia and muscle hypertrophy is similar to Thomsen's MC, but there are distinguishing features which are summarised below (Table 27.1).

27.2.3 Pathophysiology

MC is caused by mutation in the skeletal muscle voltage-gated chloride channel gene (CLCN1) on chromosome 7. In normal muscle, these chloride channels inhibit recurrent depolarisation. CLCN1 mutation leads to formation of abnormal skeletal muscle chloride channel protein. This results in uninhibited repetitive firing of muscle fibre and subsequent myotonia (Heatwole and Moxley 2007; Colding-Jørgensen 2005). In Becker's MC, both monomers of channels are affected, while in Thomsen's MC, only one monomer is affected while the other remains unaffected. This may explain clinical disparity between these two conditions caused by mutations in same gene (Heatwole and Moxley 2007). More than 160 disease-causing mutations in CLCN1 gene have been identified (Liu et al. 2015). Details of each mutation are beyond the scope of this book.

27.2.4 Investigations

Electrophysiology studies are extremely helpful in prioritising genetic testing for a patient with myotonia. On short exercise testing, recessive MC shows initial postexercise decrement, and this recovers within 60 s, i.e. Fournier pattern II (Fournier et al.

2004). Cooling the limb increases the sensitivity of short exercise tests. Thomsen's MC shows less prominent decrement and sometimes no decrement at all, i.e. Fournier pattern III (Hehir and Logigian 2013). Needle electrode examination (NEE) shows myotonic discharges in the proximal and distal muscles. Sometimes, Becker's MC may show myopathic potentials (Heatwole and Moxley 2007). CK level may be elevated. Diagnosis in these patients can be confirmed by detecting mutations in CLCN1 gene.

27.2.5 Differential Diagnosis

The differential diagnosis is brief as only a few diseases present with clinical and/or electrical features of myotonia. The following features help to differentiate MC from them (Table 27.2).

Some disorders such as inflammatory myopathy, hypothyroidism and acid maltase deficiency and medications such as colchicine and statins can display myotonia (Heatwole et al. 2013).

27.2.6 Management

In 2006, a Cochrane review documented that till the time of review, there was lack of good quality data and randomised studies on pharmacotherapy of MC. In small

Table 27.2 Differential diagnosis of MC with their key distinguishing features

Diseases	Key differentiating features
Differentials of clinical and electrical myotonia	
Myotonic dystrophy	Characteristic muscle wasting and weakness, cataract, cardiac involvement, systemic features and electrophysiological features of myopathy
Myotonia levior	Later age of onset of illness, milder symptoms and absence of muscle hypertrophy
Paramyotonia congenita	Autosomal dominant, first decade onset, myotonia predominantly involving the face and upper limbs, myotonia worsening on exercise, absence of hypertrophy, cold-induced weakness and short exercise testing show decrement lasting for prolonged period.
Hyperkalaemic periodic paralysis with myotonia	Episodes of weakness induced by fasting, cold and rest; usually spares facial muscles; mild to moderate myotonia; short exercise test may show increase in amplitudes rather than decrement and muscle biopsy shows vacuolation
Potassium-aggravated myotonia	Refer to Table 27.3
Differentials of myotonia-like symptoms but without electrical myotonia	
Schwartz–Jampel syndrome	First decade onset, severe generalised myotonia, muscle hypertrophy, blepharophimosis, skeletal and joint abnormalities.
Brody's disease	Severe muscle stiffness after exercise, muscle cramps, absence of percussion myotonia and muscle hypertrophy. Electrical myotonia is also not seen

studies, clomipramine and imipramine had shown short-term beneficial effect (Trip et al. 2006). In 2010, mexiletine (150 and 200 mg three times daily) was found to be effective as an antimyotonic agent (Logigian et al. 2010). Anecdotal case reports on improvement of myotonia with phenytoin, carbamazepine, procainamide and acetazolamide are available. These can be used carefully with appropriate monitoring for their side effects (Sharp and Trivedi 2014; Trudell et al. 1987; Berardinelli et al. 2000; Munsat 1967; Savitha et al. 2006a, b). Activity modifications and avoiding aggravating factors (exposure to cold) can help in reducing disability (Heatwole and Moxley 2007; Mankodi 2008). Recently, lacosamide and ranolazine have been found to have potential antimyotonic properties, but these need to be tested for safety and efficacy (Trivedi et al. 2014; Sharp and Trivedi 2014).

27.2.7 Prognosis

The prognosis of both forms of MC is good and there is no reduction in life expectancy. Sometimes, eyelid myotonia can be severe enough to cause disability in Thomsen's disease. Some patients with Becker's MC may develop progressive weakness which can limit ambulation (Heatwole and Moxley 2007).

27.3 Paramyotonia Congenita (PMC)

PMC is also known as von Eulenberg's disease. PMC is an autosomal dominant disorder caused by mutation in SCN4A gene, coding for skeletal muscle sodium channels. Features of myotonia begin in the first decade and predominantly involve the eyelids, tongue, face and upper limbs. The classical presentation is episodes of involuntary eye closure after washing face with cold water, 'frozen tongue' after eating ice cream and 'frozen smile' in cold environment (Fig. 27.2). With exercises, myotonia worsens, and hence it is known as paradoxical myotonia. Patient may experience episodes of weakness that last for few minutes and are triggered by cold, exercise, prolonged rest, potassium ingestion and fasting (Heatwole and Moxley 2007; Mankodi 2008; Koul et al. 2010). Patients when asked to look downwards after persistent upgaze may show 'lid lag' (Stunnenberg and Drost 2014). Unlike MC, these patients are not overtly muscular. On short exercise testing, patients with PMC show significant decrement that lasts for more than 60 s (Fournier pattern I) and is accentuated on exposure to cold (Hehir and Logigian 2013). Long exercise testing shows significant decrement that may last for an hour. Till date, over 40 mutations have been described in SCN4A gene, and genetic testing can be ordered for in appropriate clinical scenario (Heatwole et al. 2013). Patients should be encouraged to avoid triggers such as cold exposure and exercise. Medications that have a potential for patients with PMC are mexiletine, hydrochlorthiazide and acetazolamide (Statland and Barohn 2013; Benstead et al. 1987; Mankodi 2008). In a single case report, patients with R1448C mutations have been found to be responsive to

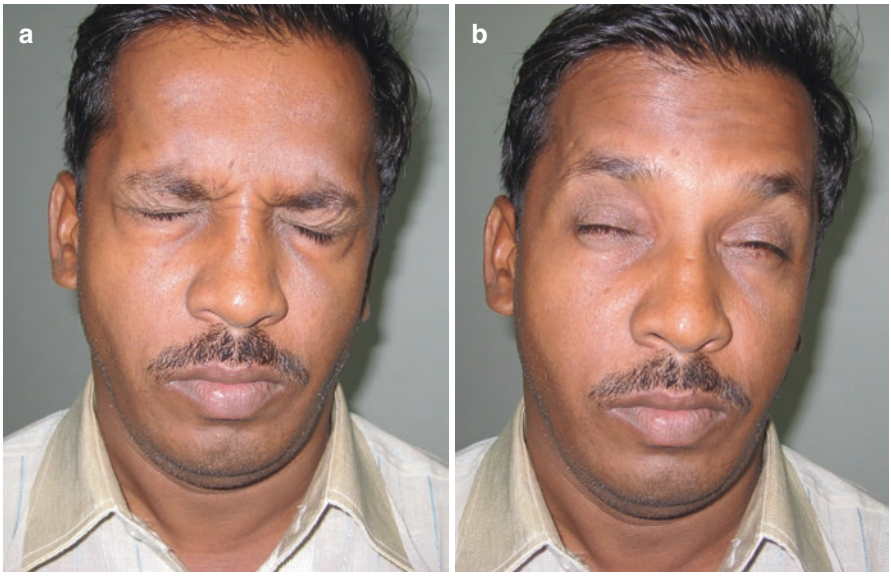

Fig. 27.2 (**a** and **b**): Eyelid myotonia in a patient with PMC

pyridostigmine (Khadilkar et al. 2010). Life expectancy is not limited, but paramyotonia and episodic weakness can be disabling and limit the quality of life (Heatwole and Moxley 2007).

27.4 Hyperkalaemic Periodic Paralysis with Myotonia

It is an autosomal dominant disorder caused by mutation in the alpha subunit of SCN4A gene, coding for skeletal muscle sodium channels. The clinical picture is dominated by childhood onset of episodic limb weakness that spares facial and respiratory muscles, lasting for minutes to hours along with features of myotonia. Weakness can be triggered by fasting, prolonged rest, cold exposure, emotional stress and potassium supplementation. Serum potassium levels are elevated during the attacks, and CK levels may also rise during attacks. During episode of weakness, compound muscle action potential (CMAP) amplitude can be attenuated. Short exercise testing shows rise in CMAPs. Long exercise testing demonstrates initial rise followed by fall in amplitude. Muscle biopsy is less informative and may show changes of vacuolar myopathy. Genetic testing helps in confirmation of the diagnosis. Management consists of avoiding trigger factors and using of pharmacological agents such as acetazolamide, thiazide diuretics and salbutamol to prevent attacks. In acute episode with life-threatening hyperkalaemia, glucose and insulin infusion may be warranted, but such situations are uncommon (Raja Rayan and Hanna 2010; Heatwole and Moxley 2007; Mankodi 2008).

Table 27.3 PAM subtypes with their key features

PAM subtypes	Key features
Myotonia fluctuans	Spontaneous fluctuations: periods of no clinical or electrophysiological evidence of myotonia lasting for hours to days Delayed-onset myotonia: exercise initially improves myotonia, but second bout of exercise after a period of 20–40 min rest produces severe myotonia Extraocular, bulbar and limb muscles can be involved; there is absence of cold-induced myotonia or episodic weakness; CK levels are raised; muscle biopsy may show vacuolar changes. Symptoms are improved by use of mexiletine or acetazolamide. Potassium-rich foods should be avoided
Acetazolamide-responsive myotonia	Unlike myotonia fluctuans, it presents as generalised myotonia that is aggravated by cold. Myotonia is painful; absence of episodic weakness; dramatic response of myotonia to acetazolamide. Potassium-rich foods should be avoided
Myotonia permanens	Severe myotonic disorder predominantly seen in the face, limb and respiratory muscles; it may or may not be aggravated by cold exposure but triggered by exercise; presence of muscle hypertrophy; severe myotonia of intercostal muscles can lead to respiratory compromise; mexiletine or tocainide can help in reducing myotonia. Potassium-rich foods should be avoided

27.5 Potassium-Aggravated Myotonias (PAM)

This group of myotonic disorders is characterised by aggravation by potassium ingestion, and these diseases are caused by sodium channel mutations. Unlike other myotonic disorders, myotonia in these diseases is not always aggravated by cold, and patients do not have prominent weakness. Key features of its three subtypes are tabulated below in Table 27.3.

27.6 Myotonia Levior

It is an autosomal dominant disorder characterised by stiffness of the grip, which is provoked by rest. As compared to Thomsen's MC, myotonia levior has later age of onset, milder symptoms and absence of muscle hypertrophy (Heatwole and Moxley 2007). Myotonia levior has been found to be caused by mutations in CLCN 1 gene. It is believed that myotonia levior is a milder variant of Thomsen's disease (Lehmann-Horn et al. 1995; Ryan et al. 2002).

27.7 Brody's Disease

This inherited disorder is caused by reduced sarcoplasmic reticulum calcium ATPase (SERCA) 1 activity due to mutation in ATP2A1 gene. This disorder is characterised by delayed relaxation of muscles after repetitive contraction and may resemble myotonia clinically. Electrical absence of myotonic discharges helps to

differentiate Brody's disease from other myotonias. Patients present with exercise-induced muscle stiffness, muscle cramps and aggravation by cold exposure that begins in early childhood. Patients do not develop episodic weakness. Examination shows delayed relaxation of muscles after repetitive contractions, but on percussion, myotonia is absent. Muscle hypertrophy is usually not prominent. CK levels are usually normal but mildly elevated CK has been reported. Severe CK elevation (often in thousands) suggests presence of associated rhabdomyolysis. Electrophysiology may show cramp discharges and myopathic potentials, but myotonic discharges are characteristically absent. Specially designed immunohistochemistry shows reduced SERCA 1 and 2 activities and genetic testing confirms the diagnosis. Stiffness may be severe enough to compromise mobility in a small proportion of patients. Few patients responded to dantrolene and verapamil. Some patients of Brody syndrome are on record, who have reduced SERCA activity but do not have mutation in ATP2A1 gene (Heatwole et al. 2013; Guglielmi et al. 2013; Voermans et al. 2012).

27.8 Case Study

Clinical Details: An 8-year old male child, born of third-degree consanguineous marriage, presented with progressive history of stiffness of both upper and lower limbs and trunk since infancy. There is history of delayed motor milestones, and he learnt to stand at 1 and ½ year of age and started to walk at 3 years of age. As he started walking, parents noticed that he was not able to walk fast or run due to stiffness of both lower limbs. Also he would stand with knees bend and cannot straighten his legs. Due to stiffness, getting up, sitting down and turning in bed also got difficult. He had difficulty in straightening both elbows, and he used to keep his arms and forearms in flexed position. Also, he was not able to stand with straight back, and he adopted a forward stooped posture since early childhood. Stiffness was severe enough to cause difficulty in opening mouth for eating, chewing and talking. His voice was slow and weak and had difficulty in opening eyelids after tight closure. This stiffness worsens, and things used to get more difficult in cold seasons, but there was no significant improvement with exercise. There was no history of cognitive deficits, flexor/extensor spasms, scissoring of limbs, weakness, wasting, cramps or fasciculations. On general examination, he was of short stature and had facial dysmorphism (Fig. 27.3), short neck, pectus carinatum and kyphosis, and passive movements across all joints were restricted. Neurological examination revealed eyelid myotonia, hypertrophy of all muscle groups and action and percussion myotonia. Rest examination was normal.

Summary: Early-onset myotonic disorder worsening with cold, muscle hypertrophy, facial dysmorphism, blepharophimosis, skeletal deformities, joint contractures, normal cognition and without any weakness.

Discussion: CK level was within normal limit. NEE confirmed presence of myotonic discharges. Presence of early-onset myotonic disorder with skeletal

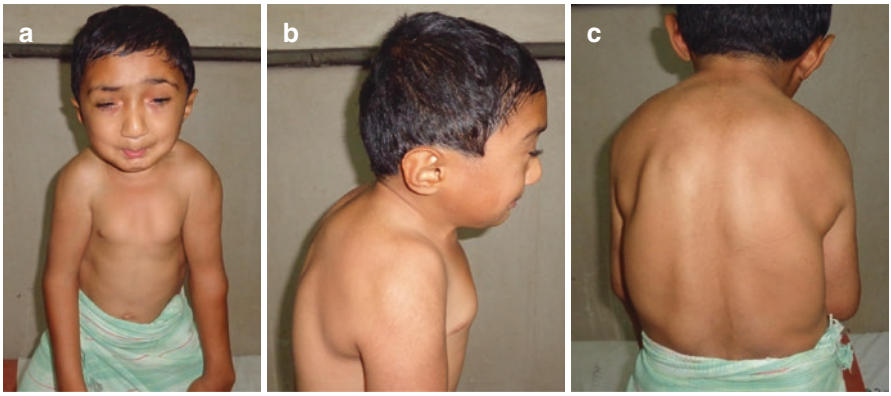

Fig. 27.3 (**a** and **b**): Facial dysmorphism (narrow palpebral fissure (blepharophimosis), low-set ears, flattened face with puckered lips and micrognathia and (**c**) hypertrophy of paraspinal group of muscles in SJS

deformities and blepharophimosis made possibility of Schwartz–Jampel syndrome (SJS) very likely (Table 27.2). However, genetic testing for detecting perlecan gene mutations was not locally available.

27.9 Schwartz–Jampel Syndrome (SJS)

SJS is a rare genetic abnormality characterised by myotonic myopathy, bone dysplasia, joint contractures and dwarfism. It is also known as chondrodystrophic myotonia. Clinical features of severe myotonia manifest at birth in the form of joint contractures, generalised hypertonia, microstomia, blepharophimosis and poor facial expressions and, sometimes, result in asphyxia. Patients fail to reach normal height and short stature can be very striking. They have a characteristic crouched stance and waddling gait due to severe stiffness. Mild mental retardation is documented in some patients. Patients develop skeletal deformities such as contractures across major joints, pectus carinatum, kyphoscoliosis, bowing of long bones, lumbar lordosis, pes planus, coxa vara and valgus ankle deformities which are evident. Muscle hypertrophy is prominent and on examination, myotonia is present. It is an autosomal recessive disorder caused by mutation in perlecan gene. Radiological changes on X-ray often document failure of development of anterior half of the vertebrae, hip dysplasia, bowing of diaphysis and abnormal epiphyseal plates. NEE may show myotonic discharges. Management consists of control of myotonic symptoms by carbamazepine, botulinum toxin for relieving symptoms in severely affected muscles, correction of skeletal deformities and physical therapy. Care has to be taken while administering anaesthesia as these patients are at risk of malignant hyperthermia (Mokete et al. 2005; Nessler et al. 2011; Ho et al. 2003; and https://rarediseases.org/rare-diseases/schwartz-jampel-syndrome/).

Key Points

When to suspect

- Grip and percussion myotonia with well-developed muscles
- None or minimal weakness
- Improvement with activity
- Absence of extramuscular manifestations
- Paramyotonia: upper body affected more, worsening with activity and cold

How to diagnose

- Clinical and electrophysiological myotonia
- Genetic studies

How to treat

- Membrane stabilisers

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Part VI

Asymmetric Sensory Motor Weakness

Individual Mononeuropathies

28

28.1 Introduction

Mononeuropathy is defined as dysfunction of a single peripheral nerve. Compression, traction, laceration, thermal or chemical injuries are common causes of mononeuropathies. Owing to anatomic factors including the proximity of nerves to osseous or fibrous structures, certain nerves are prone to extrinsic compression at specific locations. Clinical presentation and focused physical examination are vital for the anatomical localisation, which points to the probable aetiology as well. Specific electrodiagnostic studies can offer further support to the diagnostic process. Nerve imaging techniques like ultrasonography and magnetic resonance imaging are particularly helpful in analysing atypical cases. Management largely remains conservative, but surgical options are sometimes necessary for improving treatment outcomes. In this chapter, we shall discuss the common and uncommon mononeuropathies in the upper and lower limbs, respectively (Tables 28.1 and 28.2). Anatomic course, major branches and common sites of lesion of median, ulnar and radial nerves have been depicted in Fig. 28.1a, b and c, respectively.

28.2 Management

28.2.1 General Management

In most cases of entrapment neuropathies, conservative treatment is effective. The improvement is expected over time without any intervention. The management depends on factors like chronicity and severity of symptoms, the underlying mechanism and associated predisposing conditions. The fundamental aspect for designing the treatment plan involves the exact understanding of the underlying mechanism of injury and associated natural history of the condition. Conditions may continue to progress despite modifications and avoidance of predisposing factors and may require more aggressive interventions like surgical release. Splints should be used in the early stages of disease to prevent further injury. Injectable steroids with local anaesthetic at the specific site of nerve injury can result in temporary benefits.

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Table 28.1 Upper limb mononeuropathies

Common upper limb mononeuropathies

Site of lesion	Key clinical features	Key electrophysiological features	Causes
Median at wrist (carpal tunnel syndrome) Most frequent compressive neuropathy Estimated prevalence is 2% in men and 3% in women (Atroshi et al. 1999)	Tingling and numbness affecting thumb, index and middle fingers (intermittent with nocturnal worsening) Dropping objects from hand, mainly due to sensory and proprioceptive defects rather than due to true weakness in early cases Sometimes pain in the whole hand with radiation to the forearm and elbow is a feature On examination – positive Tinel/Phalen test Sensory alterations in three and half digits Wasting of thenar eminence with weakness of pincer grip	Severity is graded by **Stevens severity scale** (Stevens 1997) Mild: prolonged median sensory distal latency Moderate: prolonged median sensory and motor distal latency Severe: absent sensory response or low-amplitude motor response Very severe: absent sensory and thenar motor response and prolonged latency of lumbrical response **Sensitive tests**: useful in borderline cases Median–ulnar palmar studies (palmdiff) Median–ulnar antidromic sensory conduction to ring finger (ringdiff) Median–radial thumb antidromic sensory conduction to ring finger (thumbdiff) Combined sensory index (CSI): palmdiff + ringdiff + thumbdiff CSI >1.0 ms or greater is abnormal (Watson 2012)	Idiopathic Predisposing conditions: diabetes, pregnancy, thyroid disorders, chronic renal disease, obesity Family history is present in 30% of the cases (Elstner et al. 2006)
Ulnar neuropathy at elbow (UNE) Sites are: (1) Condylar groove (most common) (2) Cubital tunnel It is a common compressive neuropathy (Tackmann et al. 1984)	Motor weakness and atrophy of ulnar-innervated muscles and ulnar claw with extension of metacarpophalangeal and flexion at interphalangeal joints of the ring and little fingers Sensory loss and paresthesias in medial aspect of the palm (dorsal and palmar) and medial half of the fourth and the fifth digits **Wartenberg's sign**: abduction of the fifth digit due to weakness of palmar interosseous muscle **Froment's sign**: functional substitution of flexor pollicis brevis and adductor pollicis by flexor pollicis longus when attempting to grip	**ADM motor response**: it is recorded by stimulating at the elbow (AE), below the elbow (BE) and the wrist **Conduction velocity(CV)**: Ulnar motor CV across the elbow segment (AE–BE segment) < 50 m/s Ulnar motor CV across the elbow more than 10 m/s slower than the forearm segment **CMAP amplitud**e Partial conduction block: Reduction of >20% from BE to AE Significant change in CMAP configuration between BE and AE Definite partial conduction block: > 50% drop in amplitude/>40% reduction in area with less than 30% increase in duration between two stimulation sites **Short segment stimulation (inching)** >10% CMAP amplitude drop across 2 cm segment. 8 Ms. latency shift or doubling of latency across 2 cm segment (Dimberg 2012)	Trauma Deformities Previous distal humerus fracture

Table 28.1 (continued)

Common upper limb mononeuropathies			
Site of lesion	Key clinical features	Key electrophysiological features	Causes
Radial nerve Sites are: Axilla, spiral groove (most common site) (Watson and Brown 1992; Mondelli et al. 2005) PIN neuropathy	Wrist drop or finger drop with sensory loss over the dorsolateral hand and thumb, index, middle and lateral ring fingers	**Lesions above the spiral groove:** abnormality in all radial innervated muscles and abnormalities of radial SNAP **At/near spiral groove**: triceps and anconeus are spared. More distal muscles show abnormalities **PIN neuropathy**: abnormal finger and radial wrist extensor Testing of nonradial innervated muscles like PT/FCR should be done to exclude widespread process	Crutch palsy Proximal/mid humeral fracture Shoulder dislocation Saturday night palsy (extrinsic compression) Neural tumours Compression at wrist
Uncommon upper limb mononeuropathies			
Median nerve proximal to wrist The sites are: Ligament of Struthers, supracondylar spur, biceps brachii aponeurosis, between the heads of pronator teres muscle, sublimis bridge	Clinical features depend upon the site They can be differentiated from CTS by weakness of proximal median innervated muscles and the presence of sensory loss in the palmar aspect of the hand AIN presents with pure motor weakness of median innervated muscles with no sensory loss **(abnormal pinch sign)**	**Median antidromic sensory:** low amplitude, slow CV **Median motor**: low amplitude, possible partial conduction block, slow CV **Needle examination**: APB,FCR,PT,FPL,PQ – abnormal In AIN median sensory, motor studies (as we record APB) show normal findings, but needle examination of FPL and PQ yields abnormalities	Strenuous exercise Trauma Neuralgic amyotrophy Repetitive elbow motions
Ulnar neuropathy at the wrist **5 types** (Wu et al. 1985; Olney and Hanson 1988) Type I: proximal to Guyon's canal Type II: superficial terminal branch Type III: distal to Guyon's canal Type IV: hook of the hamate Type V: distal deep ulnar branch	These can be differentiated from the more common UNE lesion by preservation of sensation in medial dorsal and palmar aspects of the palm because palmar cutaneous sensory branch and dorsal ulnar cutaneous branch (DUC) originate above the wrist Motor weakness is encountered in ulnar-innervated muscles but is variable according to site of lesion	**Ulnar sensory antidromic**: abnormal in type I and II and normal in other types **Motor ADM response**: abnormal in type I and III and normal in other types DUC sensory: normal in all types **Needle examination**: ADM: abnormal in type I and III and normal in other types FDI: abnormal in all types except type II FCU and FDP: normal in all types	Ganglionic cysts Tumours Blunt injuries, with or without fracture Aberrant artery Idiopathic
Superficial radial nerve (**cheiralgia paresthetica**)	Numbness and pain in the dorsolateral hand and thumb, index and middle fingers No motor weakness	Affection of superficial radial nerve SNAP	Also known as handcuff/wristwatch palsy as it is associated with extrinsic compression of the SRN at the lateral wrist
Musculocutaneous nerve	Weakness of elbow flexion and sensory loss over the lateral forearm	Affection of biceps CMAP and LCNF SNAP	Shoulder dislocation Proximal humeral fracture External compression

(continued)

Table 28.1 (continued)

Common upper limb mononeuropathies

Site of lesion	Key clinical features	Key electrophysiological features	Causes
Axillary nerve	Weakness of arm abduction, mild weakness of shoulder external rotation Sensory loss in the 'regimental badge area'	**Motor NCS of axillary nerve:** > 50% reduction in CMAP amplitude side to side **Needle examination**: deltoid, teres minor, radial innervated muscles, upper trunk and C5, six innervated muscles	Shoulder dislocation Proximal humeral fractures External compression
Suprascapular nerve	Lesion at suprascapular notch: pain and weakness of shoulder abduction and external rotation Lesion at the spinoglenoid notch: weakness of external rotation with or without pain No sensory abnormality	**Motor NCS of suprascapular nerve:** > 50% reduction in CMAP amplitude side to side or focal slowing or conduction block at the spinoglenoid notch **Needle examination:** supraspinatus, infraspinatus and other nonscapular innervated muscles (C5/C6 roots and upper trunk of the brachial plexus)	Shoulder dislocation Hereditary brachial plexopathy Neuralgic amyotrophy
Long thoracic neuropathy	Scapular winging with difficulty in shoulder abduction or flexion	Invasive NCS of serratus anterior by needle electrode with stimulation at Erb's point Needle examination of serratus anterior (caution: pneumothorax)	Post-traumatic Post-operative procedures Hereditary brachial plexopathy Neuralgic amyotrophy

Abbreviations: *ADM* abductor digiti minimi, *CMAP* compound motor action potential, *SNAP* sensory nerve action potential, *APB* abductor pollicis brevis, *FCR* flexor carpi radialis, *PT* pronator teres, *FPL* flexor pollicis longus, *PQ* pronator quadratus, *AIN* anterior interosseous nerve, *DUC* dorsal ulnar cutaneous, *FCU* flexor carpi ulnaris, *FDP* flexor digitorum profundus, *FDI* first dorsal interosseous, *LCNF* lateral cutaneous nerve of forearm

Table 28.2 Lower limb mononeuropathies

Common lower limb mononeuropathies:				
Nerves	Key clinical features	Differential diagnosis	Key electrophysiological features	Causes
Common peroneal nerve at the fibular head	Foot drop with variable weakness of toe extension, foot eversion and ankle dorsiflexion Sensory loss at the anterolateral surface of the lower leg and dorsum of the foot Positive Tinel's sign at the fibular head	Deep peroneal nerve injury: foot drop with characteristic sensory loss in the first dorsal web space Preservation of ankle inversion is a feature of peroneal neuropathy that helps to distinguish from L5 radiculopathy	**Peroneal motor CMAP**: affected **Superficial peroneal SNAP**: affected **Needle examination** (to exclude other aetiology like sciatic nerve injury, lumbosacral plexopathy and L5 root lesion) Tibialis anterior, extensor hallucis: affected in all aetiologies Peroneus longus: affected in all aetiologies (normal in deep peroneal nerve injury) Tibialis posterior and short head of biceps: affected in sciatic, LS plexopathy and L5 root lesion Gluteus medius: affected in lumbosacral plexus and L5 root lesion Lumbar paraspinals: affected in L5 root lesion (Fridman and David 2012)	Compression at the fibular head due to trauma and application of tight casts Mononeuritis multiplex Nerve tumours, ganglion cysts
Sciatic nerve	Foot drop with radiating pain in back of the thigh and leg	Lumbosacral plexopathy, L5 nerve root lesion	**Peroneal, tibial motor CMAP**: affected **Sural, superficial peroneal SNAP**: affected except in L5 radiculopathy **Needle examination** Tibialis anterior, short head of biceps femoris: affected in all aetiologies Gluteus medius: affected in lumbosacral plexus and L5 root lesion Lumbar paraspinals: affected in L5 root lesion	Retroperitoneal/pelvic bleeding Post hip surgery Nerve sheath tumours Mononeuritis multiplex

(continued)

Table 28.2 (continued)

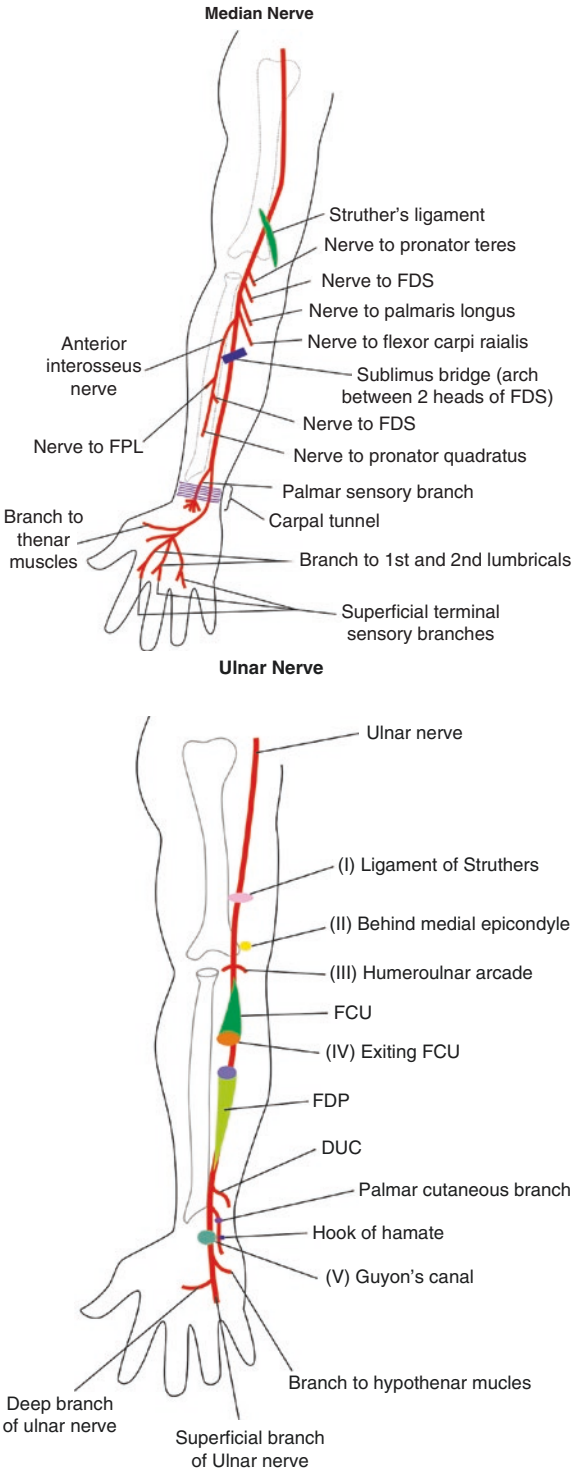
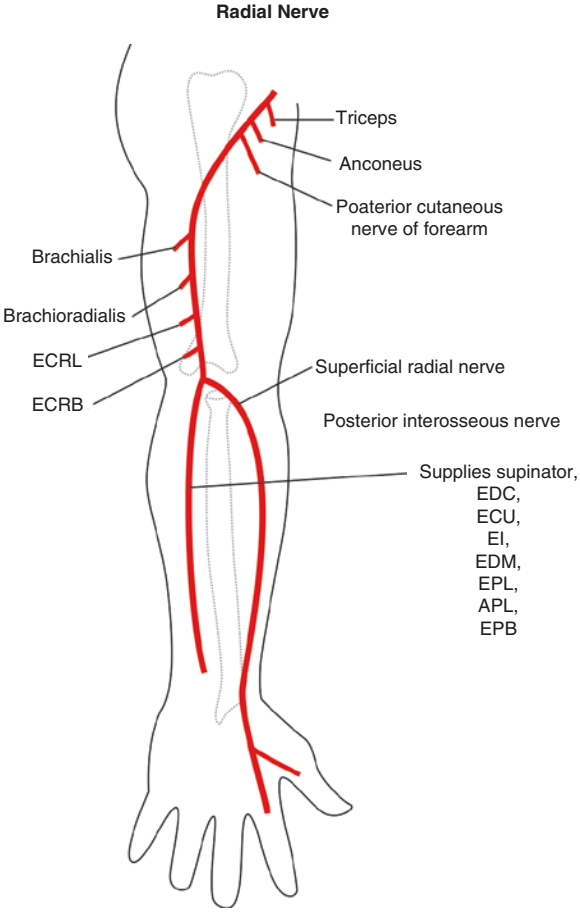


Fig. 28.1 Anatomic course, major branches and common sites of involvement of median, ulnar and radial nerves. *FDS* flexor digitorum superficialis, *FPL* flexor pollicis longus, *FDP* flexor digitorum profundus, *FCU* flexor carpi ulnaris, *DUC* dorsal ulnar cutaneous, *ECRL* extensor carpi radialis longus, *ECRB* extensor carpi radialis brevis, *EDC* extensor digitorum communis, *ECU* extensor carpi ulnaris, *EI* extensor indicis, *EDM* extensor digiti minimi, *EPL* extensor pollicis longus, *APL* abductor pollicis longus, *EPB* extensor pollicis brevis

Fig. 28.1 (continued)



28.2.2 Specific Therapies

- CTS – endoscopic release of flexor retinaculum (Korthals-de Bos et al. 2006).
- PIN neuropathy – wrist extension brace
- Cheiralgia paresthetica – neurolysis of superficial radial nerve (Stahl and Kaufman 1997).
- Meralgia paresthetica – ultrasound-guided local injection of steroids and local anaesthetic (Khalil et al. 2008).

28.3 Case Study

Clinical Details: A 27-year-old nurse presented with pain in the medial two fingers of the left hand radiating to the medial aspect of the forearm up to the elbow since 2009. Pain was severe in the day and disturbed her sleep as well. Pain used to intensify periodically for 20–25 days and subside on symptomatic treatment. There was

no history of motor weakness, but movement of fingers was restricted due to pain. Pain did not aggravate after performing overhead activities or lifting weights. She did not have neck or shoulder pains, and there was no history of wounds going unnoticed. On examination, peripheral pulses were normal, hypopigmented patches and trophic changes were not seen and Adson's test was negative. On palpation, ulnar nerve was thickened and tender. In spite of the long duration of symptoms, there were no motor or sensory deficits, and deep tendon reflexes were normal. On nerve conduction study, left ulnar digit V, DUC, ulnar-ADM and FDI were attenuated. Inching technique revealed conduction slowing along forearm. Needle electrode examination showed denervation in ulnar-innervated muscles.

Summary: Very slowly progressive, painful ulnar neuropathy above the level of wrist.

Discussion: Electrophysiological findings strongly suggested presence of ulnar neuropathy above the level of wrist. MRI neurography showed a localised, homogeneous contrast-enhancing lesion along the ulnar nerve at the level of forearm (Fig. 28.2). Possibility of neoplastic aetiology was considered. As the lesion was located at a non-entrapment site, it resulted in severe pain and was not associated

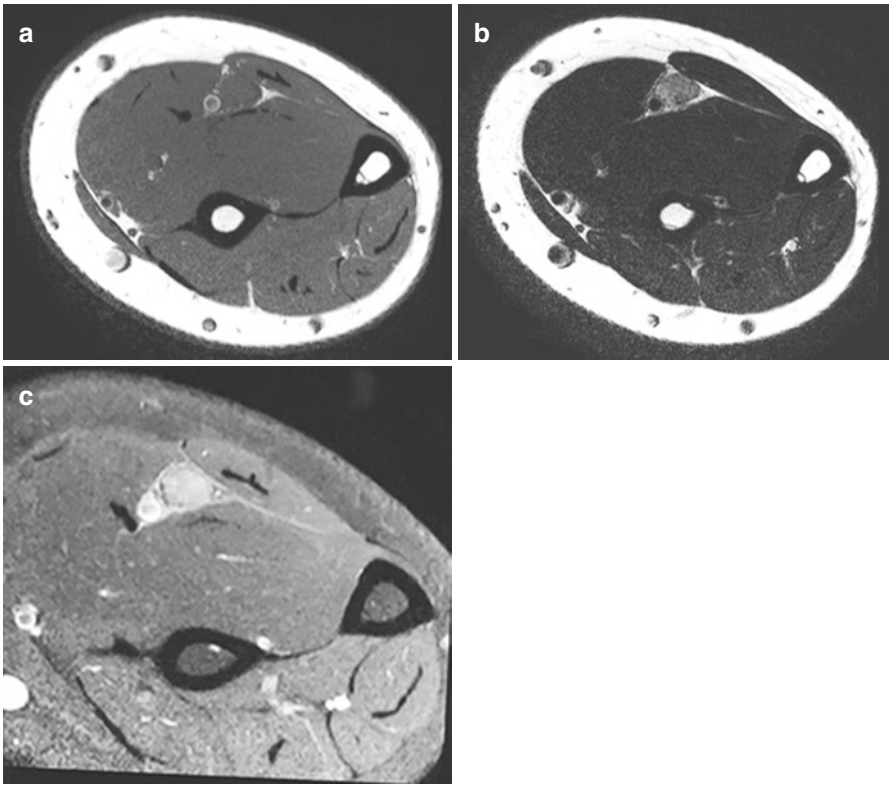
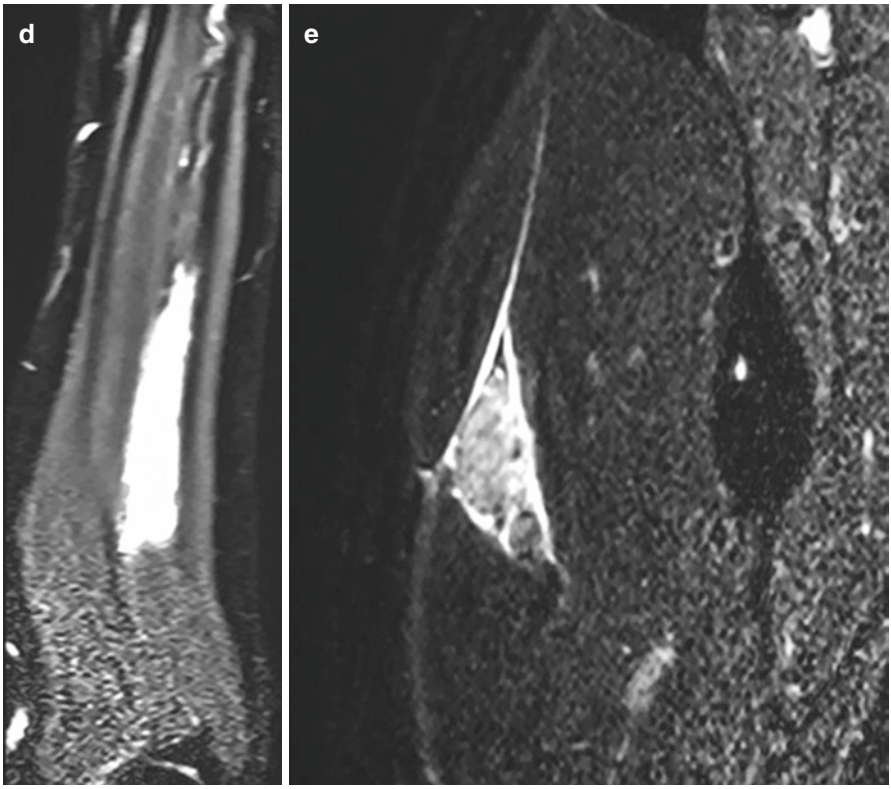


Fig. 28.2 Diffuse enlargement of ulnar nerve at the level of forearm on (**a**) T1 W and (**b**) T2 W axial forearm images. Post-contrast (**c**) axial and (**d**) coronal images show homogeneous enhancement of the ulnar nerve. On T1-STIR images (**e**), individual fascicles of ulnar nerve appear thickened (Courtesy: Department of Radiodiagnosis, Bombay Hospital, Mumbai)



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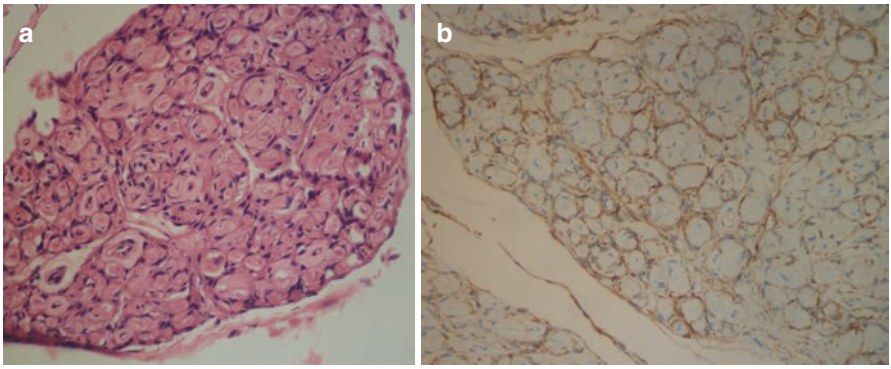

Fig. 28.3 (**a**) Pseudo-onion bulb appearance and (**b**) immunohistochemistry showing EMA positivity suggestive of perineuroma (Courtesy: Department of pathology, Bombay Hospital, Mumbai)

with major neurological deficits, and possibility of neoplastic aetiology was considered likely. Fascicular biopsy of ulnar nerve showed pseudo-onion bulb appearance which stained positive for epithelial membrane antigen (EMA) and S-100 suggestive of perineuroma (Fig. 28.3).

Final diagnosis: Perineuroma of ulnar nerve.

Key Points

When to suspect

- Single nerve involvement
- Predisposing factors (diabetes, endocrinopathies, systemic diseases)
- Known constellations, common and uncommon (Tables 28.1 and 28.2)

How to diagnose

- Clinical set of symptoms and signs
- Electrophysiologic localisation
- MRI neurography, particularly in the proximal ones
- Ultrasound examination

How to treat

- Treat predisposing condition
- Physical therapy
- Surgical intervention in select situations

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Vasculitic Neuropathy

29

29.1 Introduction

Vasculitic neuropathy is a sequential process of inflammation, thrombosis and ischemic injury to vasa nervorum, especially involving epineural arteritis of nerve. For the neurologist, it is important to know two things: (1) vasculitis can be non-systemic and localized or part of systemic disease and (2) the underlying immune process is antibody associated or immune complex driven (Marsh et al. 2013). Non-systemic vasculitic neuropathy [NSVN] patients have minimum tendency for systemic involvement and better prognosis, though patients may experience chronic pain and frequent relapses (Collins and Periquet 2004). While multi-organ involvement in primary immune-mediated vasculitides is the rule, the ANCA-associated conditions have predominant 'kidney–chest' involvement, and immune complex types have a 'kidney–skin' involvement (Schaublin et al. 2005). Vasculitic neuropathy can be classified into following (Tables 29.1 and 29.2).

Non-diabetic radiculoplexus neuropathy, Wartenberg's migrant sensory neuritis and diabetic radiculoplexus neuropathy complete the spectrum of non-systemic primary vasculitis (Lacomis and Zivković 2007; Collins et al. 2010; Marsh et al. 2013).

29.2 Epidemiology

Commonly encountered vasculitic neuropathies in descending orders are NSVN, MPA/PAN associated, rheumatoid and eosinophilic (Collins et al. 2010).

29.3 Clinical Features

This heterogeneous disease starts subacutely, having relapsing–remitting or progressive course, and shows sensory/sensorimotor impairment. A combination of asymmetric or multifocal [non-length-dependent] pain and weakness is the diagnostic

S.V. Khadilkar et al., *Neuromuscular Disorders*,
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Table 29.1 Classification of primary vasculitis

Type of vasculitis	Disease	Incidence	Features
Large vessel – granulomatous inflammation	Giant cell arteritis	Very uncommon	Headache, vision diminution, shoulder pain and raised ESR
	Takayasu arteritis	Unreported	
Medium sized – immune complex mediated	Polyarteritis nodosa (PAN)	75%	Mostly monophasic Hepatitis B involved in pathogenesis in 1/3 (case1). The most frequent findings are constitutional symptoms, neurological manifestations (typically multiple mononeuropathies), skin involvement, abdominal pain, hypertension and renal artery aneurysms. No typical autoantibody. Prognosis depends on involved organ system
	Kawasaki disease	Unreported	
Small sized – ANCA-associated	Microscopic Polyangiitis	40–80%	Onset is between 60 and 70 years Pain in abdomen Purpuric skin lesion Associated with kidney and lung diseases
	Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)	75–80%	There are three phases 1. Prodromal: asthma, rhinitis 2. Intermittent: pulmonary eosinophilic infiltrates 3. Vasculitic: skin, sinuses, joint, gastrointestinal and nerve involvement 40–70% of the patients have p-ANCA
	Wegener's granulomatosis (granulomatosis with polyangiitis)	20–25%	C-ANCA-associated disease Triad of vasculitic, glomerulonephritis and respiratory tract diseases
Small sized – immune complex mediated	Non HCV-associated essential mixed Cryoglobulinaemia	30–70%	
	Henoch–Schonlein purpura		Mainly cutaneous

clue. Patients tend to show lower limb predominance and start distally. Constitutional symptoms like fever, weight loss, malaise, fatigue, myalgias and arthralgias are present in both systemic and NSVN. Systemic examination should be done.

Table 29.2 Classification of secondary vasculitis

Disease category	Diseases	Incidence
Autoimmune conditions	Systemic lupus erythematosus	20–27%
	Rheumatoid arthritis	15–50%
	Sjogren's syndrome	2–60%
	Systemic sclerosis	Up to 30%
	Dermatomyositis	
	Behcet disease	
	Mixed connective tissue disorder	
	Malignant neoplasm	
	Cryoglobulinaemia	Upto 60%
	Sarcoidosis	
Drugs	Amphetamine, propylthiouracil, hydralazine, interferons and nonsteroidal Anti-inflammatory drugs, penicillin, allopurinol, cocaine, heroin, sulfonamides and phenytoin	
Viral infections	Cytomegalovirus, human T-lymphotropic virus 1, hepatitis, human immunodeficiency virus, herpes simplex virus, Varicella-zoster virus, Epstein-Barr virus, cytomegalovirus	
Bacterial infections	Infective endocarditis, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Salmonella typhi*, alpha haemolytic strep, Lyme, *Mycobacterium tuberculosis*, leprosy, *Treponema pallidum*	
Fungal infections	Aspergillus, coccidioides, mucormycosis, *Histoplasma capsulatum*	
Protozoa infections	*Toxoplasma gondii*, *Plasmodium falciparum*	
Radiation		
Paraneoplastic		
Malignancy		

Pain is a hallmark of vasculitic neuropathies and links and is related with nerve growth factor (Yamamoto et al. 2003). It usually begins with sensory abnormality in multiple mononeuropathies pattern. As disease advanced, pattern change to symmetric or asymmetric polyneuropathy. Examination confirms muscle weakness and reflex abnormalities in same nerve distribution. Muscular wasting develops later in the course of disease. Peroneal, tibial and ulnar nerves are commonly involved (Blaes 2015).

29.4 Pathophysiology

Commonly involved segments are watershed zones of poor perfusion in nerves, i.e. junction of proximal and middle segments (Morozumi et al. 2011).

29.5 Investigations

Table 29.3 shows consensusly recommended laboratory investigation (Collins et al. 2010)

29.5.1 Significance of Blood Tests

- Eosinophilia in Churg–Strauss syndrome.
- For AAVs: PR3/MPO-ANCAs [sensitivity 85%, specificity 99%].
- Raised ESR, high CRP, elevated RF, MPO- or PR3-ANCAs, raised β2 microglobulin, elevated VEGF and low complement.
- ANCA negativity does not exclude the diagnosis of AAV, and false positives may be seen in SLE, RA and tuberculosis.

29.5.2 Electrodiagnosis

Electrodiagnostic findings that are most supportive of a diagnosis of vasculitic neuropathy are those indicative of asymmetrical or non-length-dependent patterns of

Table 29.3 Laboratory investigations that can be required in suspected vasculitic neuropathy

Routine investigations	Specific investigations	Investigations yet to be established
CBC, AEC, ESR, CRP	ANA, RF, ANCA	Beta-2 microglobulin
Electrolytes, renal function, liver function	S. Protein immunofixation electrophoresis	Lyme antibodies
Urine analysis	Complement C3, C4, Total	DNA for PMP22 deletion
Glycated haemoglobin, 2 h GTT	Cryoglobulins	DNA for transthyretin gene
Chest X-ray	HBsAg, HCV antibodies, HIV antibodies	
Creatine kinase	Lysozyme	
Thyroid function test	VEGF	
	HCV RNA	
	CMV antigen/DNA	
	Paraneoplastic autoantibodies	
	LDH	
	High-density lipoprotein cholesterol	
	Porphyrin screen	
	Chest CT	
	Gallium 67 scan	
	Visceral angiography	
	Salivary gland biopsy	
	Lumbar puncture – CSF analysis	
	Body imaging for malignancy	

axonal neuropathy. Occasionally, conduction blocks are observed in motor nerve conduction studies done shortly after symptom onset. This transient conduction block occurs because Wallerian degeneration has not yet developed distal to the infarcted nerve, thus allowing conduction of action potentials along the distal nerve segment on distal stimulation, contrasting with the failure of conduction across the infarcted nerve fibres with proximal stimulation. With subsequent Wallerian degeneration over the ensuing week, conduction failure occurs with both proximal and distal nerve stimulation, and the apparent conduction block disappears (Said and Lacroix 2005; Dyck et al. 1987; Collins et al. 2003; Cornblath and Sumner 1991; Ropert and Metral 1990). Sensory nerve action potentials decrease in amplitude and often disappear over the 7–10 days after the ischaemic event (Wilbourn 2002).

Electrodiagnostic studies are also useful to identify a nerve that would give a good yield when biopsied. Nerves studied electrodiagnostically are sural, superficial peroneal, tibial and peroneal in lower limbs and median, ulnar and radial in upper limbs. The sural and superficial peroneal sensory studies should be compared side to side. A 50% inter-side difference in amplitudes recorded from the same nerve is generally regarded as a meaningful difference.

29.5.3 CSF Study

Indication of lumbar puncture in suspected vasculitic neuropathy patients:

1. Proximal limb involvement
2. Clinical possibility of sarcoidosis
3. Suspected malignancy
4. Positive meningeal signs
5. Electrophysiology shows mixed picture of axon loss and demyelination
6. Electrophysiology shows proximal involvement

29.5.4 Histopathology

It is considered as gold standard for diagnosis of vasculitic neuropathy.

29.5.4.1 Biopsy Site

Nerve with moderate involvement by clinical EDX study or radiographic criteria should be selected for biopsy. Simultaneous muscle biopsy should be considered if there is easy access to muscle. A combined nerve–muscle biopsy gives positive result in 60–70% of cases (Marsh et al. 2013). One study suggests that distal leg muscle biopsy gives better yield (Bennett et al. 2008).

Concomitant skin biopsy is also known to enhance the yield for vasculitis. Sometimes it only shows perivascular inflammation without vasculitis (Lee et al. 2005; Uceyler et al. 2010). Amongst patients of unclear aetiology of neuropathy, who undergo nerve biopsy, approximately 1% show vasculitis (Kissel et al. 1985; Davies et al. 1996).

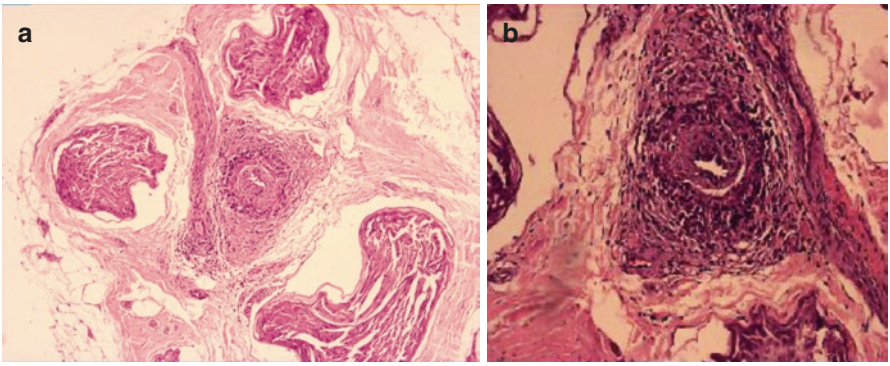

Fig. 29.1 (**a**) 10× and (**b**) 40×: Haematoxylin and eosin preparation showing cellular infiltration in all layers with narrowing of vascular lumen and fibrinoid necrosis (Courtesy Department of Pathology, Bombay Hospital, Mumbai)

A new multifocal neuropathy developing in patients who already have an established diagnosis of systemic vasculitis (that included biopsy of another involved organ), nerve biopsy can be avoided. Nerve biopsy is necessary to diagnose patients with suspected classic NSVN (Collins et al. 2003). Nerve biopsy might not be necessary for diagnosis of many cases of LRPN (lumbosacral radiculoplexus neuropathy), DLRPN (diabetic lumbosacral radiculoplexus neuropathy) or DCRPN (diabetic cervical radiculoplexus neuropathy), but it can be useful in cases with atypical features, such as a progressive clinical course.

29.5.4.2 Findings

- Transmural inflammation with vascular damage
- Inflammation of vessels less than 40–70 m without vascular damage
- Immunoglobulin M, C3 or fibrinogen deposit
- Deposit of haemosiderin
- Asymmetric nerve fibre involvement
- Predominant active degeneration of axons
- Muscle fibres show necrosis, regeneration or infarct

(Collins et al. 2010) (Fig. 29.1)

29.6 Differential Diagnosis

- If a patient has a pure motor, entirely proximal and symmetric neuropathy, think of other differentials.
- NSVN (non-systemic vasculitic neuropathy): for diagnosis of NSVN.
- Rule out other aetiology of neuropathies, systemic involvement and other rheumatologic diseases.
- Biopsy to confirm vasculitis.
- Differential diagnosis of multiple mononeuropathies:

Axonal injury:

- Diabetes mellitus
- HIV
- Leprosy
- Sarcoidosis
- Vasculitis

Demyelination:

- Multifocal motor neuropathy
- Multifocal acquired demyelinating sensory and motor neuropathy
- Multiple compression neuropathies
- Hereditary neuropathy with liability to pressure palsies
- MND with sensory involvement (Devigili et al. 2011)

- Differential diagnosis of painful neuropathies:

Neuropathies: Diabetic, HIV, toxic, uremic, vasculitic, amyloid, paraneoplastic, cryptogenic small fibre, hereditary (HSAN), Fabry's disease and plexopathy.

Please refer to section on case study for key distinguishing features to differentiate between different causes of mononeuritis multiplex.

29.7 Management

Progressive and active diseases need immediate attention, while improving or stable disease may need regular follow-up (Collins et al. 2010). The first step in management is to identify aetiology and treat it.

There are two main phases in the treatment of PNS vasculitis: remission induction therapy [corticosteroid + cyclophosphamide (CYC)/methotrexate (MTX)/rituximab] and maintenance therapy [corticosteroid + CYC/MTX/azathioprine (AZT)] (Marsh et al. 2013; Guillevin and Pagnoux 2007; Collins and Kissel 2005).

29.7.1 Remission Induction Therapy

It is an initial treatment that results in resolution of the manifestations of active vasculitis.

Various immunosuppressive agents, their doses, side effects and monitoring are summarised in Table 29.4.

Patient on immunosuppressants should be advised to receive pneumococcal and influenza vaccination. Live vaccines should generally be avoided. Rapidly progressive vasculitic neuropathy and patient who progress on CS monotherapy requires other immunosuppressant in addition to corticosteroid. Rapidly progressive means when new deficits develop within 1 month of presentation. When rapid effect is needed, intravenous methylprednisolone 1 g/day for the first 3 days, then oral prednisolone at 1 mg/kg/day can be used (Marsh et al. 2013).

Table 29.4 Salient features of various immunosuppressive agents that can be useful in vasculitic neuropathy

Drug	Dose	Side effects	Monitoring	Care
Corticosteroids (CS)	Oral: 1 mg/kg/day, the dose is then gradually tapered; however, the dose should not go below 15 mg/day for the first 3 months. When a dose of 15 mg/day is reached, the steroid taper is continued at a slower rate	Glucose intolerance, osteoporosis, peptic ulcer, weight gain, myopathy and reactivation of latent tuberculosis	Blood pressure, Blood glucose, weight Chest X-ray	Bisphosphonate, calcium, vitamin D and proton pump inhibitor
Cyclophosphamide (CYC)	15 mg/kg (max dose 1.2 g) initial 3 doses are given at every 2 weeks, then interval should be of 3 weeks till remission, then for another 3 months 2. Oral: 2 mg/kg/day for 3 months followed by 1.5 mg/kg/day for another 3 months 3. Intravenous CYC dose adjustment depend on age, renal function and complete blood count	Bone marrow suppression, haemorrhagic cystitis and serious systemic infections, increases the risk of malignancy, particularly lymphoma, leukaemia, transitional cell carcinoma of the bladder and non-melanomatous skin cancer	A complete blood count should be checked weekly after the first dose and then every 2 weeks. Urinalysis is routinely carried out prior to each dose	Mesna is administered intravenously immediately before the intravenous CYC infusion. Two further oral doses are given at 2 and 6 h after the start of the infusion to reduce the urotoxic side effects of a metabolite of CYC. Prehydration with a litre of normal saline is usually given before the CYC pulse. If a patient develops haematuria, discontinue cyclophosphamide, refer to urologist, evaluate for haemorrhagic cystitis or transitional cell carcinoma. *Pneumocystis jiroveci pneumonia*: All patients should receive prophylaxis co-trimoxazole 960 mg given orally three times a week. Antiemetic medication on a 'when required' basis for the initial 48 h. CYC treatment is associated with infertility and the possibility of egg/sperm harvesting should be discussed with appropriate patients

Table 29.4 (continued)

Drug	Dose	Side effects	Monitoring	Care
Methotrexate (MTX)	Oral: Start with 10 mg once a week, gradually increasing to 20–25 mg once a week over 1–2 months if tolerated	Nausea, vomiting, leucopenia, ulcerative stomatitis, rash, dizziness, fatigue, increased susceptibility of infection and bone marrow suppression. Uncommon side effects: interstitial pneumonitis	Baseline chest X-ray Routine blood monitoring for full blood count, liver and renal function throughout treatment	Folic acid (5 mg once a week): reduce the incidence of gastrointestinal and hepatic toxicity. In symptomatic patients for interstitial pneumonitis, methotrexate should be temporarily withheld, while pulmonary function tests, chest imaging and pulmonary consultation are obtained to exclude an infectious cause
Azathioprine (AZT)	Oral: 2–3 mg/kg/day	An acute hypersensitivity reaction can occur shortly after initiation and consists of nausea, diarrhoea, malaise, myalgias, rash and fever. Delayed side effects include increase susceptibility to infection, hepatotoxicity, pancreatitis and bone marrow suppression. There is a small increased risk of neoplasia	Complete blood count and liver function weekly in first month, then every month for 6 months and then every 3 monthly	The hypersensitivity symptoms resolve with discontinuation
Rituximab	375 mg/m^2	Hypotension, chills, dyspnoea, fever, headache, gastrointestinal disturbances, flushing, angioedema, urticaria, pruritus, respiratory disease and infections, including progressive multifocal leukoencephalopathy		Acetaminophen and antihistamine premedication

Usually in clinical practice 6–10 pulses CYC are required over a period of 3–6 months. The pulse of intravenous CYC is only given if the WCC on the day of the pulse is >4 × 10^9/l and neutrophils >2 × 10^9/l. If this is not the case, the pulse is postponed until the WCC is in range, normally rechecking full blood count on a weekly basis. Plasma exchange in addition to the standard treatment regimens (with oral prednisolone and intravenous CYC) has been used in life-threatening conditions (Lapraik et al. 2007). RITUXVAS and RAVE have shown similar efficacy of rituximab when compared with cyclophosphamide for remission induction in AAV (Jones et al. 2010; Stone et al. 2010; Jayne et al. 2000).

29.7.2 Remission Maintenance Therapy

Objective evidence of absence of worsening and sustain improvement over 6 months indicate clinical remission.

Azathioprine: 2 mg/kg/day as effective as CYC 1.5 mg/kg/day.

29.7.3 Newer Drugs

B cell therapy: rituximab

T cell therapy: alemtuzumab [anti-CD52 antibody], abatacept [co-stimulatory blockade with CTLA4-Ig], gusperimus (Jayne 2013)

Anti-cytokine drugs: etanercept [anti-TNF], tocilizumab [anti-IL-6 receptor antibody], mepolizumab [anti-IL-5 antibody] and bortezomib [proteasome inhibitor]

29.8 Prognosis

Remission induction rate: 90% by 6 months

5-year survival rate: 75%

Relapse rate: 50% (Marsh et al. 2013)

Markers of poor prognosis in vasculitis:

- Advanced renal impairment at presentation.
- Presence of c-ANCA with anti-proteinase 3 (which is highly suggestive of Wegener's granulomatosis) rather than p-ANCA with anti-myeloperoxidase (more commonly seen in microscopic polyangiitis and Churg–Strauss syndrome). MPA has poor outcome compare to CSS (Koike and Sobue 2013).

A five-point score has been designed to evaluate prognosis (Guillevin et al. 2011).

29.9 Case Study

Clinical details: A 46-year-old male presented with progressive asymmetrical painful weakness of both upper limbs, 6 months before presentation. Illness started with low-grade fever and dry cough. He was evaluated, diagnosed and treated for dengue fever and enteric fever based on his serological investigations, but there was no improvement. Subsequently, he noticed difficulty in buttoning his shirt, beginning with the right hand and later affecting the left hand as well. He was not able to perceive objects fully in palmer aspects of both hands. He significantly lost weight. There is no lower limb weakness, bowel and bladder symptoms, nor any cranial nerve involvement. He did not remember being exposed to drugs and toxins. Family history was not contributory. Examination confirmed wasting, asymmetric sensory motor weakness, neurogenic tremor and depressed reflexes in both upper limbs. In view of asymmetrical painful neurogenic weakness, EDX study was performed. It showed evidence of multifocal sensory motor axonal neuropathy. His investigations showed eosinophilia. His ANA, ANA profile, APLA, rheumatoid factor, sputum and BAL for AFB, serology for HBsAg, HCV and HIV were negative. His blood sugar, renal function tests, thyroid function tests, ECG, CSF, USG abdomen and MRI of the brain and spine were normal. His p-ANCA was positive, and CT thorax showed bronchopneumonia.

Discussion: This patient had painful sensory motor multiple mononeuropathies. Differentials of multiple mononeuropathies (mononeuritis multiplex) are listed in Table 29.5.

Clinical, electrophysiological and biochemistry profile strongly suggest possibility of vasculitis. Nerve biopsy helps to confirm neuritis and also rule out close differentials. He underwent right superficial radial nerve biopsy which showed

Table 29.5 Differential diagnosis of mononeuritis multiplex with important clinical clues

Diseases	Clinical clues
Leprosy	Usually painless (pain can occur in lepromatous leprosy), h/o painless wounds, hypoasthetic and hypopigmented skin patches and thickened nerves
Diabetes mellitus	Painful, predominant sensory neuropathy and mild motor manifestations can occur
HIV	Painful, sensory >> motor neuropathy
Vasculitis	Painful, sensory and motor affection, may be present with features of systemic vasculitis, elevated ESR, autoimmune panel may show a specific marker
MADSAM	Sensory–motor, upper limb predominant, proximal + distal polyneuropathy. Prominent sensory symptoms in extremities, more common in females fourth decade
MMN	Painless, pure motor neuropathy affecting upper limbs
Multiple compression neuropathies	Painful, sensory–motor, multiple mononeuropathies. Electrophysiology shows conduction slowing across compression sites. It occurs in diabetes, hypothyroidism and HNPP

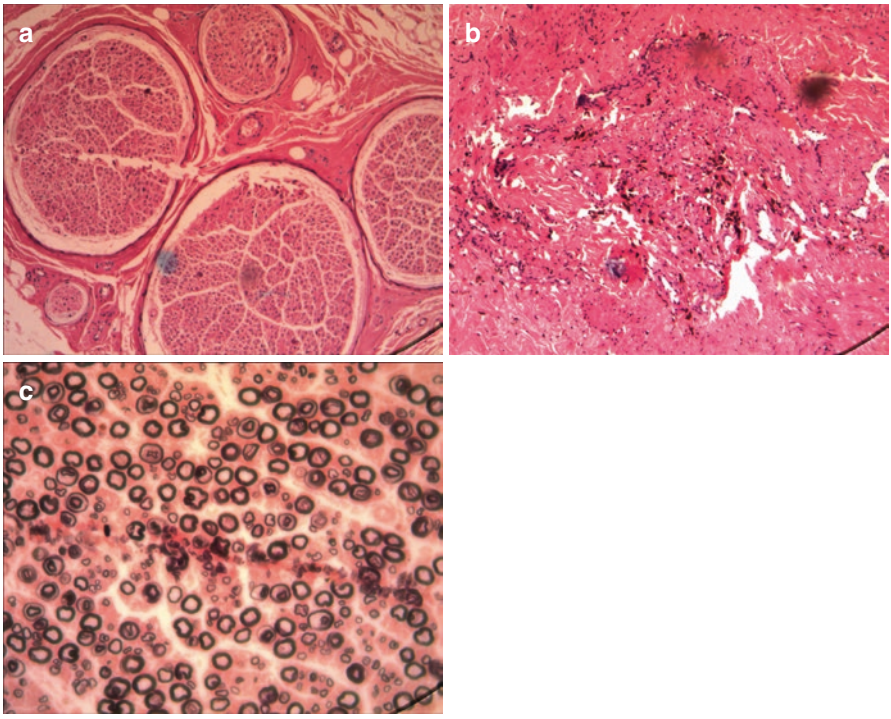

Fig. 29.2 (**a**) HE stain, 10× showing mild perivascular inflammation around small-sized epineurial vessel; (**b**) HE stain, 40× demonstrating hemosiderin depositions around the blood vessel (indicating vascular damage) and (**c**) Kpal stain for myelin reveals many regenerating clusters (*marked by arrow*) indicating chronic axonal neuropathy (Courtesy: Dr. Dilip Jethwani)

moderate chronic, non-uniform axonal neuropathy with mild perivascular inflammation and hemosiderin deposition suggestive of vasculitic neuropathy (Fig. 29.2).

Rheumatological evaluation showed systemic vasculitis process (CT thorax and ENT examination and eosinophilia).

Final diagnosis: ANCA-associated vasculitis

Key Points

When to suspect

- Painful mononeuritis multiplex
- Systemic features like skin rashes, joint changes and hypertension

How to investigate

- Acute phase reactants
- Immunological markers
- Electrophysiology to confirm mononeuritis multiplex, particularly when the clinically symmetrical or extensive, and to choose the site for biopsy

How to treat

- Immunotherapy (Table 29.4)
- Therapy for neuropathic pain

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Multifocal Acquired Demyelinating Sensorimotor Neuropathy

30

30.1 Introduction

MADSAM neuropathy is a variant of CIDP. It is characterised by multifocal demyelination in the nerve trunks (Kuwabara et al. 2015). In 1982, Lewis, Sumner and colleagues described several patients with asymmetric chronic demyelinating sensorimotor neuropathy. These patients had clinical presentation of mononeuritis multiplex, and their electrophysiological studies showed multiple conduction blocks. This group of patients exhibited a favourable response to corticosteroids (Lewis et al. 1982). Oh and colleagues compared patients with MADSAM with those having the pure motor multifocal neuropathy (MMN) and described the differences in these two neuropathies (Oh et al. 1997).

30.2 Clinical Features

MADSAM patients present with an insidious, slowly progressive and chronic sensorimotor mononeuropathy multiplex. Symptoms usually begin in the hands and go on to involve the leg and foot areas. Patients can present initially with involvement of single nerves that progress to confluent and symmetrical involvement (Verma et al. 1990). Up to one-half of patients with MADSAM may evolve into a typical pattern of generalized CIDP (Viala et al. 2004). Paraesthesia and pain are common sensory phenomena in these patients. The condition can affect cranial nerves including the optic nerves. Deep tendon reflexes are diminished or absent in the involved segments (Saperstein et al. 1999).

30.3 Pathophysiology

Cellular immunity is affected in MADSAM as opposed to typical CIDP.

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30.4 Investigations

Over 80% of patients have elevated protein content in the cerebrospinal fluid (Saperstein et al. 1999). Unlike MMN, MADSAM neuropathy is not associated with anti-GM1 antibodies.

As in MMN and CIDP, nerve conduction studies in MADSAM neuropathy show features of multifocal demyelination at non-entrapment sites, and proximal conductions can be slowed. The main difference between MMN and CIDP is the early and consistent involvement of the sensory NCS. Ultrasound protocol to differentiate CIDP, MMN, MADSAM and vasculitic or paraproteinemic neuropathy is as follows (Kerasnoudis et al. 2016):

- According to the Bochum ultrasound score, the cross-sectional area of ulnar nerve in Guyon tunnel, ulnar nerve at the upper arm, radial nerve in the spiral groove and sural nerve near the gastrocnemius muscle are evaluated.
- If BUS ≥2 points, then CIDP can be the possible diagnosis.
- If BUS <2, either of median nerve in forearm or ulnar nerve in forearm or tibial nerve at the ankle is affected, then MMN can be possible diagnosis.
- If none of the above-mentioned sites are pathological and either of median nerve in carpal tunnel or ulnar nerve at the elbow is affected, then MADSAM can be possible diagnosis.
- If none of above-mentioned nerves are affected, then possibility of vasculitic or paraproteinemic neuropathy should be considered.

30.5 Differential Diagnosis

- MMN: normal sensory, normal CSF, anti-GM1 antibodies
- HNPP: history of recurrent compressive palsies, foot deformities or family history of compression or generalized neuropathies

Please refer to chapter on vasculitic neuropathy and leprosy for differential diagnosis of mononeuritis multiplex.

30.6 Management

The mainstays of therapy have been corticosteroids and IVIg. Prednisolone can be started in the doses of 1–2 mg/kg initially on daily basis till improvement begins. Later, alternative day regimen can be adopted to reduce the unwanted effects. After substantial improvement is achieved, doses can be tapered. Complete stoppage of prednisolone has to be done under strict monitoring as relapses are frequent. In a study done by the Washington University neuromuscular group, intravenous methylprednisolone therapy was evaluated (1 g a day for 3–5 days for 4–8 weeks). This pulse steroid therapy had fewer side effects as compared to daily oral prednisolone

therapy and can be considered as an option in suitable candidates. MADSAM is a chronic immunological disease, and hence long-term immunosuppression is required. Hence, a steroid-sparing agent needs to be introduced, and the guidelines are similar to those given in the chapter on CIDP.

IVIg therapy is known to give favourable therapeutic response in over 70% of patients and is easy to administer, and side-effect profile is favourable. However, repeated admissions are required for the administrations. Plasma exchange (PE) is used in MADSAM patients as a rescue therapy when the weakness is severe. PE results are faster than IVIg but wane rapidly. Hence, PE, unlike IVIg, cannot be used as a single therapy and is combined with prednisolone. Presently both IVIg and PE have been credited with level A recommendations, and corticosteroids are at level C (Van den Bergh et al. 2010).

30.7 Prognosis

While MADSAM is a modifiable disorder and the disability can be limited, the course of the disease is chronic, fluctuating and indolent. Long-term use of immunosuppressant medication needs careful clinical and biochemical monitoring. Overall, the prognosis of MADSAM patients is not as favourable as typical CIDP.

Key Points

When to suspect

- Asymmetric painless sensorimotor neuropathy

How to investigate

- Electrophysiology showing demyelinating asymmetric neuropathy
- Elevated CSF protein levels
- Exclude secondary causes

How to treat

- Chronic immunotherapy

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Brachial Plexopathy

31

31.1 Introduction

Brachial plexus is a connecting link between the spinal cord and upper limb. Neurologists frequently encounter a variety of diseases affecting brachial plexus. Trauma to the brachial plexus is perhaps the most common cause in clinical practice. Neuralgic amyotrophy [NA] is a multifocal, immune-mediated, inflammatory peripheral nervous system disorder of brachial plexus. True neurogenic thoracic outlet syndrome is a rare disorder caused by angulation and stretching of the lower plexus by a band or rib (Ferrante 2012a, b) or by scalene muscle hypertrophy (Katirji and Hardy 1995). A traction-induced lower plexopathy can follow sternotomy operations like the coronary artery bypass (Lederman et al. 1982). Lower plexus invasion is frequent in apical lung tumours like bronchogenic carcinoma. Common causes of brachial plexopathy have been summarised in Table 31.1.

Table 31.1 Causes of brachial plexopathy

Traumatic brachial plexopathy
Idiopathic brachial plexopathy (neuralgic amyotrophy)
Hereditary brachial plexopathy (HMSN, hereditary brachial neuritis)
Neurogenic thoracic outlet syndrome
Radiation-induced brachial plexopathy
Intrinsic tumours (Schwannoma, neurofibroma)
Extrinsic tumours – benign(desmoids tumours, lipomas, lymphangiomas, haemangiomas and perineuronal cysts)
Extrinsic tumours – malignant (recurrences of breast cancer, apical lung tumours, lymphomas, metastatic lymphadenopathy, osteosarcomas and Ewing's sarcomas)

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31.2 Epidemiology

Compared with infraclavicular plexopathies, supraclavicular plexopathies are commoner, are associated with closed traction injuries and tend to be severe because greater force is required to produce them (Wilbourn 2005). Upper plexopathies are more common than middle or lower plexopathies, tend to occur in isolation and commonly follow trauma, especially closed traction (Brunelli and Brunelli 1992).

31.3 Clinical Features

31.3.1 Supraclavicular Plexopathy

The clinical presentation depends on site of involvement, i.e. supraclavicular or infraclavicular. The deficits of supraclavicular plexopathies tend to resemble those encountered in roots lesions as the lesion is proximal. On the contrary, infraclavicular plexus lesions produce deficits in distribution of one or more terminal nerves. In patients who have sustained trauma, palpation of the neck, axilla, supraclavicular, infraclavicular, and scapular regions for space occupying lesions, bony abnormalities, tenderness and Tinel's sign are important. The supraclavicular plexus is further divided into upper plexus, middle plexus and lower plexus. Clinical features of supraclavicular lesions are summarised below in Table 31.2.

Table 31.2 Clinical features of supraclavicular plexopathy

Site of lesion	Clinical features
Upper plexus	Weakness occurs in the distribution of affects C5–C6 myotomes affecting external rotation and abduction at shoulder joint, elbow flexion and supination and, to a lesser degree, forearm pronation and extension. Notably, biceps and brachioradialis reflexes may be depressed. Sensory loss occurs over the lateral aspects of the arm, forearm (lateral cutaneous nerve of forearm) and the dorsolateral aspect of the hand (superficial radial nerve), especially the thumb. Traumatic upper plexus lesions most commonly occur due to traction injuries, caused by the sudden force to shoulder. Such injuries are frequently encountered in sports contact and vehicular accidents.
Middle plexus	Middle plexopathies, causes sensory loss and weakness in C7 distribution, it produces weakness of elbow extension and pronation, wrist extension and flexion and, to a lesser degree, finger extension. In these patients, the triceps reflex may be depressed
Lower plexus	Lower plexopathies produce sensory loss affecting medial aspect of the arm, forearm and hand; weakness occurs in C8–T1 myotomes; the finger flexor reflex may be affected and Horner syndrome may be noted. Due to peculiar anatomy of lower plexus, the T1 axons are affected more than the C8 axons particularly in thoracic outlet syndrome. Although most patients have a long history of sensory symptoms along the medial aspects of the arm and forearm, they tend to present with motor symptoms such as progressive weakness and wasting of the forearm and small muscles of hands, leading to loss of hand dexterity (Gilliatt 1984). An important clue to thoracic outlet syndrome is preferential involvement of thenar muscles, as they are largely innervated by T1 fibres. In post sternotomy plexopathy, the C8 anterior primary ramus is affected, which contains sensory axons primarily destined for the ulnar nerve and hence their disruption mimics an ulnar neuropathy

(Zimmerman and Weiland 1991)

31.3.2 Neuralgic Amyotrophy

Most patients with neuralgic amyotrophy have a unilateral onset, often involving the dominant limb. Weakness and wasting are predominantly proximal as this condition has a predilection for motor nerves like the long thoracic, suprascapular, axillary, musculocutaneous nerves innervating shoulder girdle muscles, followed by the anterior and posterior interosseous nerves innervating forearm muscles. It can also preferentially affect individual motor branches to selective muscles (Ferrante and Wilbourn 2008). It frequently spares nerves outside the distribution of brachial plexus, e.g. spinal accessory and superior laryngeal nerves. Less commonly, mixed nerves carrying both sensorimotor fibres are affected like the radial, median and ulnar nerves are less frequently affected. Involvement of pure sensory nerves is extremely rare (Ferrante and Wilbourn 2008). Neuralgic amyotrophy is an extremely painful condition. It is acute in onset and typically occurs over the lateral aspect of the shoulder. Pain occurs usually after awakening from sleep and then maximizes, but it can be severe enough to awaken patient from sleep. Pain often occurs in the distribution of inflamed nerves. It takes few weeks for the pain to resolve and is replaced by dull ache. Following pain, weakness becomes evident and is followed by atrophy. The condition can rarely be recurrent, at times after similar triggers (Ferrante and Tsao 2013).

31.3.3 Hereditary Neuralgic Amyotrophy (HNA)

It is inherited as an autosomal dominant pattern. Severe pain followed by repeated episodes of paralysis and sensory disturbances in an affected limb is the hallmark of this condition. HNA is genetically linked to chromosome 17q25, where mutations in septin-9 [SEPT9] gene have been found (Klein et al. 2002). Certain points that favour HNA over idiopathic form are no gender differences, higher chances of recurrence, more common affection of cranial nerves and presence of dysmorphic features (Chance and Windebank 1996).

31.3.4 Rucksack Paralysis (Pack Palsy or Cadet Palsy)

It is a rare cause of upper plexopathy which occurs in individuals who wear rucksacks or similar devices. Direct pressure from straps leads to compression of upper plexus. Most patients develop unilateral weakness in an upper plexus distribution, correlating with rucksack usage. Although occurrence of sensory symptoms is common, this condition is usually painless. The probability of developing rucksack paralysis is more with increased weight, duration of wear, presence of unpadded strap and lack of waist belt.

31.3.5 Neoplastic Plexopathy

Lung and breast cancers are amongst the common neoplasms to cause metastasis to brachial plexus. Severe pain over the shoulder girdle radiating to the inner aspect of the upper limb is the hallmark of metastatic plexopathy. Due to proximity of axillary lymph nodes draining the lung and breast are in proximity to lower plexus, it is predominantly affected with neoplastic plexopathy. Apart from motor and sensory deficits in distribution of lower plexus, Horner's syndrome is an additional clue to neoplastic plexopathy as it occurs due to involvement of the T1 root or inferior cervical sympathetic ganglion.

31.3.6 Radiation Plexopathy

Lung, breast and other tumours occurring in the chest, neck and axillary region may require treatment with radiation, which may result in brachial plexopathy. In patients with neoplasms, apart from metastasis, radiation plays a vital role in causing brachial plexopathy. Many factors play a role in development of brachial plexopathy such as radiation dose, technique and concomitant chemotherapy. The common tumours which are associated with radiation-induced plexopathy are breast carcinoma followed by lung carcinoma and lymphoma. It has to be differentiated from metastatic plexopathy. Points that favour radiation-induced plexopathy are predominant affection of the upper trunk, less pain and presence of myokymic discharges.

31.4 Pathophysiology and Anatomy

Each brachial plexus is a densely packed structure containing abundant axons as it supplies whole upper limbs (Wilbourn 2005). It is comprised of five roots (C5–T1), three trunks (upper, middle and lower), six divisions (anterior and posterior of each trunk), three cords (medial, lateral and posterior) and five terminal nerves (Ferrante and Tsao 2013). Anatomically, based on its relation to clavicle, brachial plexus is divided into supraclavicular (roots and trunks), retroclavicular (divisions) and infraclavicular (cords and terminal nerves) plexus. Supraclavicular plexus is further divided into:

- Upper–upper trunk + C5 and C6 roots
- Middle–middle trunk + C7 root
- Lower–lower trunk + C8 and T1 roots

Anatomists and nerve surgeons differ in their opinion as far as 'root' is considered. Anatomists refer to pre-ganglionic fibres (ventral and dorsal root) as 'root'. The surgeons include both pre-ganglionic (ventral and dorsal root) and post-ganglionic fibres (anterior and posterior primary rami and the mixed spinal nerve) as 'root'(Wilbourn 1997). The thoracic outlet extends from the supraclavicular

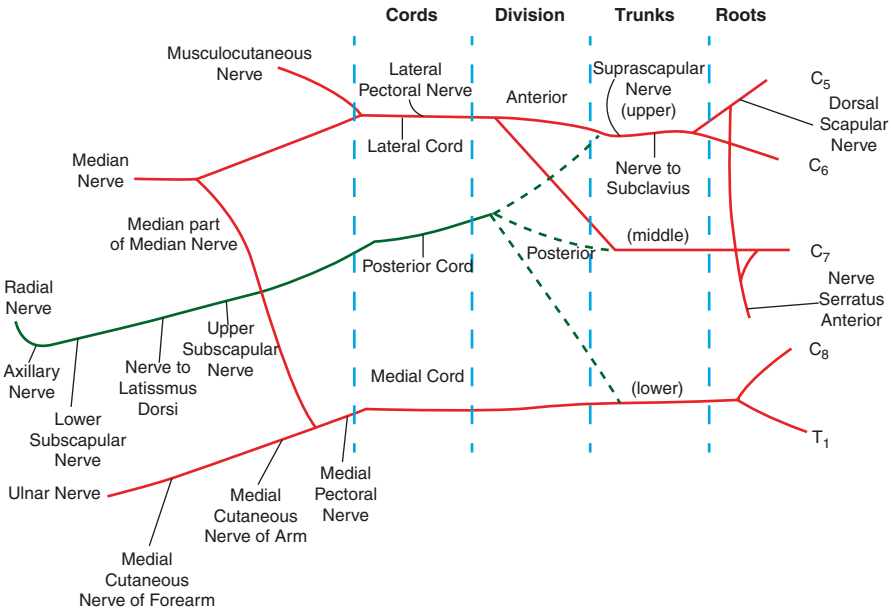

Fig. 31.1 Composition of brachial plexus

fossa to the axilla and includes the area between the clavicle and the first rib. Figure 31.1 shows the formation of the brachial plexus.

31.5 Investigations

31.5.1 Electrodiagnosis

Electrodiagnosis is important to identify, localise and characterise brachial plexus lesions. It also helps to determine elements of brachial plexus involved and pathologically characterise lesions. Most importantly it assesses severity and prognosis. It is important to understand the anatomy of brachial plexus from electrophysiological point of view. As discussed earlier, brachial plexus is divided into many segments, namely, roots, trunk, division and cords. Each segment has its own motor (muscle innervated by that segment) and sensory (sensory nerve fibres contained in it) domain which can help in localisation. For example, the medial cord of the brachial plexus will contain as its muscle domain the muscles innervated by ulnar nerve, medial pectoral nerve and medial head of median nerve. Its sensory fibres will be from the medial cutaneous nerve of the forearm (100%) and ulnar nerve supplying the little finger (100%). Detecting such pattern of abnormality helps in the localisation of the site of the lesion (Ferrante and Wilbourn 2002). It is also important to understand that single muscle receives its nerve supply from nerve, cord, trunk and roots. Thus muscle domain is tested from a distal to proximal level, e.g.

the extensor indicis muscle is innervated by the radial nerve, posterior cord, lower trunk and C8 and T1 roots (Manshukhani 2013). First-hand knowledge of these domains of each segment is important in localisation of brachial plexus lesion, which is summarised in Tables 31.3 and 31.4.

Table 31.3 Nerve, cord, trunk and root supply of muscles of the upper limb

Trunks	Cord	Nerve	Supply	Root value
Lower	Medial	Medial part of median nerve Ulnar nerve Medial cutaneous nerve of forearm Medial pectoral nerve Medial cutaneous nerve of arm	APB ADM; FDI Sensory supply to medial forearm Pectoralis muscles Sensory supply to medial arm	T1 > C8 C8 > T1 C8, T1 C7, C8 and T1 T1 > C8
	Posterior	Radial nerve	Extensor indicis	C8, T1
Middle	Posterior cord	Radial nerve Thoracodorsal nerve	Extensor digitorum communis Triceps Latissimus dorsi	C7, C8 C7 C7
Upper	Posterior cord	Radial nerve Axillary nerve	Brachioradialis Deltoid	C6 C5, C6
	Lateral cord	Musculocutaneous nerve Lateral pectoral nerve Lateral part of median nerve	Biceps Pectoralis muscles Flexor carpi radialis	C5, C6 C5, C6 C6, C7
	–	Suprascapular nerve	Supraspinatus	C5, C6

Note: Long thoracic and dorsal scapular nerves which supply serratus anterior and rhomboideus, respectively, directly arise from roots
APB Abductor pollicis brevis, *ADM* Abductor digiti minimi and *FDI* First dorsal interossei

Table 31.4 Area wise sampling of brachial plexus

Area examined	Nerve	Cord (%)	Trunk (%)	Root (%)
Thumb	Median	Lateral (100)	Upper (100)	C6 (100)
Index finger	Median	Lateral (100)	Middle (80); upper (20)	C7 (80); C6 (20)
Middle finger	Median	Lateral (80); medial (20)	Middle (70); lower (20); upper (10)	C7 (70); C6 (10); C8 (20)
Lateral forearm	Lateral antebrachial cutaneous	Lateral (100)	Upper (100)	C6 (100)
Dorsum hand	Radial	Posterior (100)	Upper (80); middle (20)	C6 (100)
Little finger	Ulnar	Medial (100)	Lower (100)	C8 (100)
Medial forearm	Medial antebrachial cutaneous	Medial (100)	Lower (100)	T1 (100)

Once the lesion has been localised to roots, it is important from a treatment and prognosis point of view to differentiate between pre-ganglionic and post-ganglionic sites. Sensory nerve action potential (SNAP) is a sensitive test to localise the site of the lesion as it is attenuated or absent in post-ganglionic lesions and remains unaffected in pre-ganglionic pathology. However, once SNAP is absent, it does not return to normal with regeneration and, thus, is not helpful for predicting recovery in brachial plexus lesions (Ferrante and Wilbourn 2002, 1995; Wilbourn 1997). Compound muscle action potential (CMAP) amplitude of distal muscles starts to drop by day 3 following the injury, and it reaches its lowest level by day 7 as compared to SNAP, which tends to show abnormality later than a drop in CMAP amplitude (Wilbourn 1997). Hence, one should be aware that the severity of the lesion can only be judged after 7 days of the injury. When CMAP amplitude is normal from a clinically weak muscle after 7 days of injury, it suggested neuropraxic lesion and, thus, favourable prognosis (Ferrante and Wilbourn 2002; Ferrante 2012a, b). Subsequent increase in amplitude correlates with reinnervation of affected muscle. To evaluate nature of injury in proximal muscles, needle electrode examination (NEE) is required to document axon loss, its severity and whether roots are affected or not. NEE also helps to document recovery in the form of nascent units and unstable polyphasic units (Nandedkar 1997). Following the muscle domains as determined by Ferrante and Wilbourn, it is possible to accurately localise the site of the lesion (Ferrante and Wilbourn 2002) (Table 31.2). Needle EMG detects reinnervation well before clinical recovery is noted (Daube and Rubin 2009).

Electrodiagnostic study can also help to assess the aetiology in some scenarios. For example, predominant T1 involvement in greater severity than that of C8 is essentially pathognomonic of neurogenic thoracic outlet syndrome (Ferrante and Wilbourn 1995). Sensory nerve conduction study showing abnormal ulnar (fifth digit) response with normal medial antebrachial cutaneous response points towards possibility of post median sternotomy.

31.5.2 Radio Diagnosis

Once the site of lesion is localised, imaging modalities like X-ray, CT and MRI neurography can help to identify the nature of lesion. Cervical rib and other bony abnormalities can be easily identified by plain films. It may be surprising to note that in patients with bilateral cervical ribs, the smaller rib is usually on the symptomatic side (Cherington et al. 1995). MR neurography can help to show abnormalities in plexus. It can help to demonstrate plexus involvement in neoplastic, inflammatory, traumatic and radiation-induced plexopathy. The main MRI findings of radiation-induced plexopathies are diffuse uniform thickening of the radiated segment of the plexus, poorly demarcated fat interfaces, hypointense on T1-weighted images, hyperintense on T2-STIR images and moderate to extensive gadolinium enhancement. Concomitant involvement of the adjacent soft tissues favours the possibility of radiation plexopathy. In the chronic stage, plexus appears hypointense on both T1- and T2-weighted images suggestive of fibrosis (Boulanger et al. 2013; Fig. 31.2).

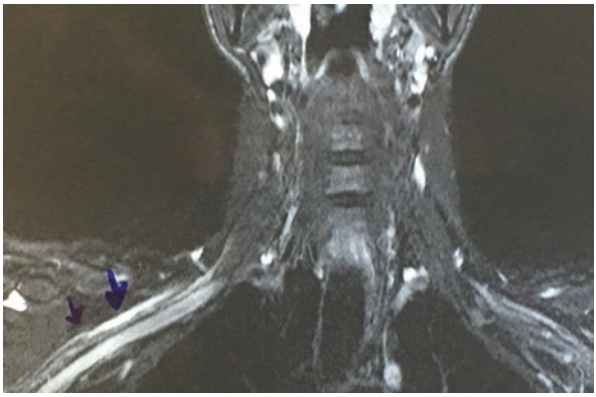

Fig. 31.2 Atrophy of right shoulder and biceps

31.6 Differential Diagnosis

Differential diagnosis of brachial plexopathies have been mentioned in Table 31.5.

Table 31.5 Differential diagnosis

Condition	Key differentiating features
Rotator cuff tendinitis and glenohumeral bursitis	Pain localised to deltoid area and lateral upper arm; abduction and anteflexion painful during active and passive movements (Van Eijk et al. 2016)
Acute cervical radiculopathy	All symptoms usually in a single root distribution Pain and weakness often come together Objective sensory changes are common Triggers, e.g. trauma

31.7 Management

Management of brachial plexopathy includes addressing the underlying aetiology, symptomatic treatment and rehabilitation. The pain in NA can be severe and may not respond to first-line nonsteroidal anti-inflammatory agents. In these situations, opioids may have to be added (van Alfen and van Engelen 2006). A Cochrane Review on the treatment of NA noted that administration of high-dose prednisone within the first month from attack onset helps to shorten the duration of pain and improve functional recovery in some patients (van Alfen et al. 2012; van Eijk et al. 2009). Anecdotal case reports have used intravenous immunoglobulin, but its role is still not clear (Johnson et al. 2011; Nakajima et al. 2006). Physical therapy focuses on training of scapular coordination endurance training of shoulder muscles, which has to be tailored to individual patient, as a proportion feel worse after physical therapy (Ijspeert et al. 2013). The treatment of thoracic outlet syndrome is essentially surgical, supported by physical therapy (Ferrante 2012a, b). Surgery often

halts the disease progression with some reversal of symptoms. Post median sternotomy plexopathy is treated conservatively, and typically, a full and rapid recovery follows, but causalgic pain develops in some patients (Ferrante 2014).

31.8 Prognosis

Although NA is reported to show good recovery after 2–3 years in large majority of patients, some studies have described a far less optimistic prognosis (van Alfen and van Engelen 2006; van Alfen et al. 2009). Prognosis depends on severity of deficits and underlying aetiology. Traumatic brachial plexus lesions with concomitant vascular injury tend to have a worse prognosis. Favourable features in pancoast tumour include absence of metastasis elsewhere such as scalene or mediastinal lymph node involvement and pain resolution following preoperative radiation (Ferrante 2009). As the pathology is predominantly of demyelination in post median sternotomy plexopathy, the prognosis is good. Even when axon loss occurs, the lesion is usually incomplete, favouring reinnervation. In rucksack paralysis, as demyelination predominates, recovery is rapid. When axon loss predominates (one third of patients with this condition), the outcome varies with lesion severity (Wilbourn 2005).

31.9 Case Study

Clinical Details: A 55-year-old male presented with acute onset of right upper limb proximal weakness, severe enough to cause inability to lift the arm and flex his elbow. It was associated with neck pain and shoulder pain. Over a period of next few days, he noticed progressive wasting of the right arm (Fig. 31.3). This was associated with tingling sensation over his right shoulder. On examination, there was weakness

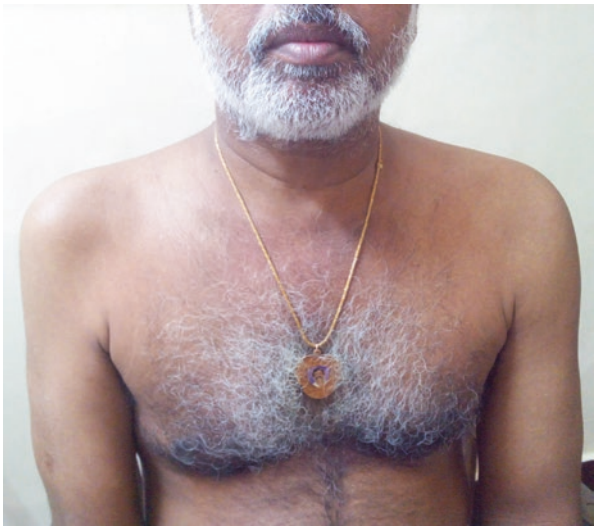

Fig. 31.3 Post-contrast T1-weighted coronal section shows thickening and enhancement of brachial plexus in hypertrophic plexitis (Courtesy Department of Radiology, Bombay Hospital, Mumbai)

of right deltoid, biceps, supraspinatus, infraspinatus, rhomboids and brachioradialis muscles. Biceps and supinator jerks were absent on right side, while other deep tendon reflexes were normal. There was sensory loss over the right shoulder.

Summary: 55-year-old male presented with acute onset, painful weakness followed by wasting in distribution of C5–C6 myotome.

Discussion: Both C5, C6 radiculopathy and upper brachial plexopathy can present with acute onset of painful weakness and wasting distribution of C5–C6 myotomes. Electrophysiology was not much helpful on day 4 of presentation. X-ray cervical spine showed erosion and sclerosis of C4–C7 vertebral bodies (Fig. 31.4). To further evaluate root and plexus, imaging of cervical spine and plexus was performed. MRI cervical spine showed extensive patchy signal loss in the right C4–C7 vertebral levels (Fig. 31.4).

Complete loss of signal in foramen of C5–C7 vertebrae was intriguing. Space occupying lesions are known to produce altered signal intensity on MRI. However, the blood flow in vessels can cause flow voids and produce apparent loss of signal as well. Auscultation of the neck demonstrated long systolic bruit, suggesting vascular causes. To evaluate blood vessels of the spinal cord, digital subtraction angiography (DSA) was done, which showed arteriovenous fistula (AVF) arising from the right vertebral artery (Fig. 31.5). Vertebral artery coiling was carried out and it showed resolution of AVF (Fig. 31.5). Patient had significant improvement in pain but residual weakness persisted.

Final diagnosis: Vertebral artery AV fistula presenting as cervical radiculopathy.

Only few cases of vertebral artery AVF presenting as cervical radiculopathy have been described in literature (Kohno M). Though uncommon, it is important to consider AVF in differentials of radiculopathies due to space occupying lesion. Loss of signal on MRI was a radiological clue to AVF.

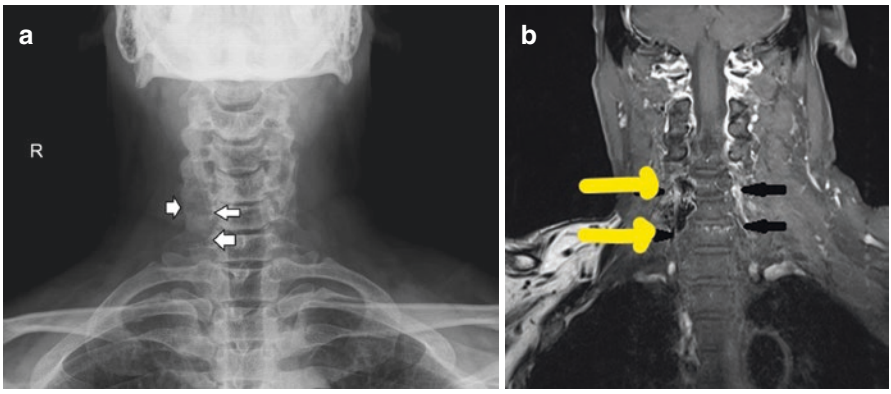

Fig. 31.4 (**a**) Anteroposterior view of X-ray cervical spine shows widening of foramen transversarium (*white arrow*) of the right C4–C7 cervical vertebrae with pressure erosion and sclerosis of the adjacent vertebral bodies suggestive of slow growing chronic pathology in foramen transversarium. (**b**) MRI cervical spine coronal image shows extensive patchy signal loss (*yellow arrow*) in the right C4–C7 vertebral level with thickening of right C5–C7 nerve roots

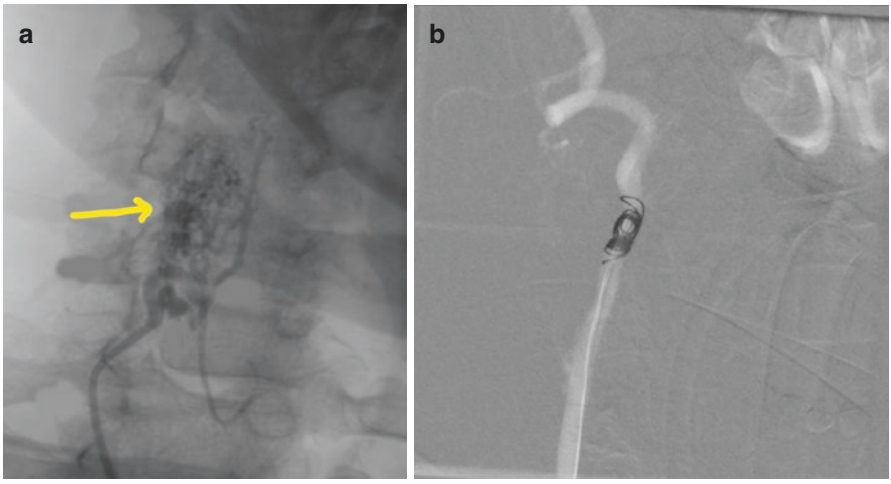

Fig. 31.5 (**a**) DSA shows feeder right vertebral artery with nidus (*yellow arrow*) and draining vein in the right C4–C7 vertebral level. (**b**) Resolution of AVF after coiling of feeder vessel (Dr. Sharad Ghadge, Consultant Radiologist, Mumbai)

Key Points

When to suspect

- Weakness and/or sensory deficits in one upper limb
- Associated conditions like neoplasms, trauma, radiation

How to investigate

- Electrophysiology
- MRI neurography

How to treat

- As per cause

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Lumbosacral Plexopathy

32

32.1 Introduction

Lumbosacral plexus provides nerve supply to the pelvis and lower limbs. Lumbosacral plexopathies (LSP) result from various disease processes such as trauma, infection, neoplasm, radiation, hematoma or other retroperitoneal masses, stretch or mechanical injury and ischaemia or inflammations (Table 32.1). In a proportion of cases, exact disease processes remain elusive, the idiopathic category. The clinical hallmark of LSP is severe, neuropathic painful sensorimotor deficits in the lower limb. Electrophysiological studies can be useful to differentiate plexopathies from radiculopathies. Magnetic resonance imaging (MRI) neurography can further help to confirm plexopathy, identify the extent of lesion and elucidate the underlying aetiology. Some diseases such as diabetes and neoplastic infiltration cause a combined involvement of plexus as well as roots and nerves. Hence, the term 'radiculoplexoneuropathy' seems appropriate for such involvements. It is important for clinicians to be aware that potentially life-threatening disorders can present with plexopathies, and delay in diagnosis and treatment can lead to severe morbidity and mortality (Dyck and Thaisetthawatkul 2014; Planner et al. 2006; Robbins et al. 2016; Van Alfen and van Engelen 1997).

S.V. Khadilkar et al., *Neuromuscular Disorders*,
https://doi.org/10.1007/978-981-10-5361-0_32

Table 32.1 Causes of lumbosacral plexopathy

Subgroups	Diseases
Trauma	Pelvic fracture, sacroiliac joint injury, gunshot wound, traumatic dislocation of hip, hip surgeries and compression of plexus from foetal head against pelvic brim during labour
Neoplasm	*Malignant invasion*: Colon, cervix, ovary, urinary bladder and prostate gland *Metastasis*: Breast, lung and lymphoma *Benign*: Neurofibroma, perineuroma, schwannoma and malignant peripheral nerve sheath tumours *Small round cell undifferentiated tumours*: Rhabdomyosarcoma, primitive neuroectodermal tumour (PNET) and neuroblastoma
Non-neoplastic space occupying lesions	Retroperitoneal haematoma secondary to coagulopathy such as haemophilia and aneurysmal dilatation of distal aorta
Inflammatory/ immune-mediated/ vasculitis	Diabetic lumbosacral radiculoplexus neuropathy (LSRPN) also known as diabetic amyotrophy, chronic inflammatory demyelinating polyneuropathy (CIDP), postsurgical inflammatory neuropathy
Infections	Psoas or pelvic abscess secondary to local gastrointestinal, urinary or pelvic infections
Miscellaneous	Endometriosis, radiation exposure, piriformis syndrome, amyloid infiltration
Idiopathic	Nondiabetic lumbosacral radiculoplexus neuropathy (LSRPN) is the lumbosacral variant of brachial plexus neuropathy

32.2 Epidemiology

The exact incidence and prevalence of LSP is not known. Common causes of LSP are inflammatory, traumatic and neoplastic disorders.

32.3 Clinical Features

LSP is characterised by acute to subacute onset of neuropathic pain in the distribution of lumbosacral plexus. Pain is usually severe and is the most disabling symptom of LSP. Sensory disturbances manifest as paresthesias, dysesthesias which sometimes progress to complete sensory loss. This is associated with loss of muscle strength that can vary from mild paresis to severe weakness. Involvement of the upper lumbar plexus (L1–L4) leads to pain and paresthesias in the low back, hip and thigh and weakness of hip flexors, hip adductors and knee extensors. Knee jerk is frequently absent, and ankle jerk is preserved in upper lumbar plexopathy. Lower lumbosacral plexopathy (L4–S1) presents as foot drop due to weakness of tibialis anterior. Plantar flexors, hip flexors and toe movements are affected. Patients experience sensory complains in posterior thigh, foot and leg. Plexopathies are predominantly unilateral, but some diseases can lead to bilateral plexus involvement. Key clinical features of various aetiologies of LSP are described in Table 32.2.

Table 32.2 Clinical features of various causes of LSP

Subtypes	Clinical features
Trauma	Acute onset; painful paresis in distribution of peroneal nerves commonly followed by gluteal, tibial and obturator nerves; symptoms due to associated injuries to local pelvic organs such as urinary bladder, intestinal perforation and vascular injury; postpartum plexopathy commonly presents with foot drop due to involvement of lower lumbosacral plexus
Neoplasm	Usually unilateral; but bilateral involvement can occur secondary to widespread metastasis; subacute onset of pain in back, hip, posterior aspect of thigh and buttocks; pain aggravated on lying down or during sleep should arouse suspicion of neoplastic aetiology; motor deficits and sensory complaints depend on level of plexus involvement (upper or lower) but commonly whole lumbosacral plexus is affected
Non-neoplastic space occupying lesions	Acute onset of unilateral pain in the lower back or flank; motor deficits in lower limb. Compressive plexopathies are severely painful and underlying aetiology can be often life-threatening
Inflammatory/ immune-mediated/ vasculitis	*Diabetic LSRPN*: Acute onset of pain in thigh, weakness of hip flexors, hip adductors and knee extensors and absent knee jerk; associated with unintentional weight loss; unilateral at onset but can involve bilateral lumbosacral segments; patients may go on to develop lower lumbosacral plexopathy; most patients improve but recovery tends to be slow and may be incomplete
Infections	Subacute onset of pain; systemic symptoms such as fever, weight loss, malaise and night sweats; psoas abscess presents with upper lumbar plexus involvement, while gluteal abscess frequently causes lower lumbosacral plexopathy
Radiation exposure	Effect of radiation is delayed and symptoms can start from few months to many years after exposure; total dose of radiation and presence of comorbid illness such as diabetes are the common risk factors for radiation-induced plexopathy; patients present with insidious onset muscular weakness and atrophy, either unilateral or bilateral; pain and sensory symptoms in radiation plexopathy are milder as compared to plexopathy of neoplastic origin; patients have symptoms due to fibrosis secondary to radiation exposure such as bowel/bladder involvement and vertebral necrosis and collapse; careful examination of affected muscles may reveal myokymia
Idiopathic	Presentation is very similar to diabetic LSRPN

Dyck and Thaisetthawatkul (2014), Khadilkar et al. (2015), Delanain et al. (2012), You et al. (2011), Katirji et al. (2002), Kutsy et al. (2000) and Dyck et al. (2001)

32.4 Relevant Anatomy and Pathophysiology

Lumbosacral plexus is located within the substance of psoas major and is formed by ventral rami of L1–S4 nerve roots. Lumbosacral plexus gives rise to multiple nerves such as sciatic, gluteal, femoral, obturator nerves, etc. which subserve sensory and motor functions of the lower limb and pelvic girdle muscles. Anatomically, it can be divided into upper lumbar plexus (L1–L4 +/− T12) and lower lumbosacral plexus (L5–S4). The branches of lumbosacral plexus and their supply have been summarised in Table 32.3. Lumbosacral plexus and its branches have been depicted in Fig. 32.1.

Table 32.3 Branches of lumbosacral plexus and their motor and sensory supply

Division of plexus	Branches	Motor and sensory supply
Upper lumbar plexus (L1–L4)	Iliohypogastric nerve (T12–L1), ilioinguinal nerve (L1), genitofemoral nerve (L1–L2), lateral femoral cutaneous nerve (L2–L3), femoral nerve (L2–L4) and obturator nerve (L2–L4)	*Motor*: Hip flexion; hip adduction and knee flexion *Sensory*: Groin; thigh (anterior, medial and lateral aspects) and medial aspect of leg up to ankle
Lower lumbosacral plexus (L5–S4)	Superior gluteal nerve (L4–S1), inferior gluteal nerve (L5–S2) and sciatic nerve (L4–S3, posterior femoral cutaneous nerve (S1–S3) and pudendal nerve (S1–S4)	*Motor*: Hip abduction; hip extension; knee flexion; all movements at ankle joints and of toes *Sensory*: Whole of the leg and foot (except medial aspect of leg); posterior thigh; buttocks and perianal region

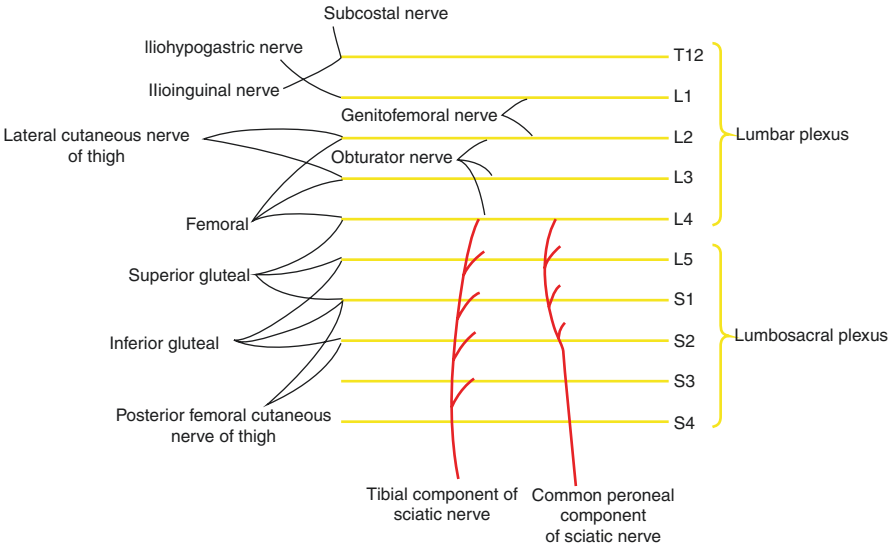

Fig. 32.1 Composition of lumbosacral plexus

Various disease processes lead to LSP by different mechanisms as described below:

- Neoplastic disorders: Direct neural infiltration, retroperitoneal lymph node enlargement and compression of plexus, perineural spread of tumours
- Infections: Compression of plexus by abscess formation
- Trauma: Laceration of nerve endings in pelvic fracture, stretch injury in postpartum LSP
- Non-neoplastic space occupying lesions: Direct compression of plexus
- Inflammatory/immune-mediated, e.g. diabetic LSRPN: Microvasculitis leading to axonal changes and segmental demyelination

(Dyck and Thaisetthawatkul 2014; Planner et al. 2006 and Dyck and Windebank 2002)

32.5 Investigations

Investigations are directed to confirm plexopathy, identify the extent of lesion (additional root or nerve involvement) and elucidate the underlying cause. Electrophysiological and radiological tests help in localisation of lesion. Radiological tests such as MRI of lumbosacral plexus are of diagnostic importance, when trauma, neoplasm, diabetic and compression of plexus are suspected to be the cause. Blood tests, cerebrospinal fluid examination and imaging-guided biopsy can be useful in selected cases. Tests that can aid in diagnosis are summarised in Table 32.4.

Table 32.4 Key investigations for evaluation of LSP

Nerve conduction studies (NCS)	Reduction in amplitude of compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs). F-wave latencies may be delayed on affected side. Involvement in distribution of at least two different roots and at least two different nerves is characteristic of plexopathy
Needle electrode examination (NEE)	NEE shows spontaneous activity, e.g. fibrillations and neurogenic motor unit potentials. Presence of myokymic discharges is characteristic of plexopathy. Presence of fibrillation potentials in paraspinal muscles occur in radiculoplexus neuropathy
Imaging modalities	*MRI neurography*: It is useful in differentiating benign from malignant processes in a case of suspected neoplastic plexopathy. Radiation plexopathy and neoplastic infiltration can be differentiated on MRI findings. MRI studies are indispensable for guiding the operative management of tumours. Uniform thickening and contrast enhancement of plexus occur in diabetic and nondiabetic LSRPN and CIDP (Fig. 32.2). In traumatic injury, MRI localise the site of entrapment and site of neuroma formation. MRI is diagnostic for evaluation of disease process such as abscesses, haematomas or vascular malformations in suspected compressive plexopathy *Positron emission tomography (PET)*: In neoplastic plexopathy, extent of malignant process within and outside the nervous system
Blood tests	Complete blood count, blood sugar, glycosylated haemoglobin, ESR, ANA, anti-SSA, anti-SSB, HIV, immunofixation and clotting profile should be considered
Cerebrospinal fluid (CSF) examination	In diabetic and nondiabetic LSRPN and CIDP, CSF protein is elevated and cell count remains normal. Neoplastic infiltration of roots can lead to rise in cell count in CSF
Nerve or tissue biopsy	Targeted fascicular or nerve biopsy is sometimes useful to delineate the pathological process such as microvasculitis in diabetic and nondiabetic LSRPN and for confirmation of diagnosis in neoplastic infiltrations. In abscess, pus aspiration can help to isolate the pathogenic organism. Sometimes, biopsy of space occupying lesion causing compression can be useful to confirm the diagnosis. Imaging modality is indispensable in localising the site of biopsy

ESR erythrocyte sedimentation rate, *ANA* antinuclear antibodies, *HIV* human immunodeficiency virus

Dyck and Thaisetthawatkul (2014), Robbins et al. (2016) and Kimura (2013)

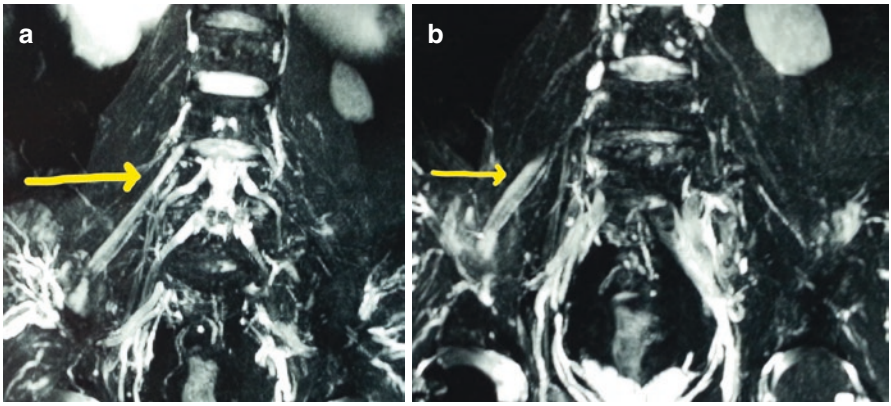

Fig. 32.2 (**a**) and (**b**) L3 root and lumbar plexus (*arrow*) hypertrophy and contrast enhancement on post-contrast T1-weighted coronal images in a patient with nondiabetic LSRPN

Table 32.5 Differentiation between plexus and root lesion

Plexus lesion	Root lesion
Mostly unilateral	Often asymmetric and bilateral
Onset with severe pain followed by moderate to severe sensorimotor deficits, e.g. neoplastic, diabetic LSRPN, etc.	Back pain, radicular pain and variable motor-sensory deficits, e.g. degenerative disc disease
Sensory loss in distribution of multiple nerves	Sensory loss in root distribution
In LL, both high lumbar and LS roots involved	Disc disease more often causes lower lumbar and sacral nerves
Common aetiologies: Diabetic LSRPN, infiltration and trauma	Disc prolapse [most common], SOL in spinal canal and trauma
SNAP amplitude reduced to absent	SNAP amplitude remains normal in most cases
NEE shows affection of muscles in distribution of at least two roots and two nerves	NEE shows affection of muscles in root distribution

32.6 Differential Diagnosis

As clinical presentation of plexopathy and radiculopathy can be overlapping, it can often be a challenging task for the clinicians to differentiate between them. Both may coexist. Following points can help to differentiate plexopathy and radiculopathy (Table 32.5).

32.7 Management

Therapy of LSP revolves around treatment of underlying disease, management of severe neuropathic pain and physical therapy to mitigate motor disability (Table 32.6).

Table 32.6 Management of LSP

Treatment of underlying disease	*Nondiabetic LSRPN*: Immunotherapy has been used with varying benefits in patients with LSRPN. Only one randomised trial has been conducted to evaluate the efficacy of intravenous methylprednisolone (IVMP) in LSRPN. IVMP showed improvement in pain and sensory symptoms but failed to improve motor deficits. Other anecdotal reports have reported significant improvement within 6 months of treatment with 50–60 mg corticosteroids or IVMP. Rate and degree of improvement tend to be greater with the use of immunotherapy. Similarly, no controlled trials on the use of intravenous immunoglobulin (IVIG) or plasma exchange (PE) have been published. Few case series have shown significant improvement with IVIG or PE *Diabetic LSRPN*: Since clinical features of both diabetic and nondiabetic LSRPN are similar, therapy for them does not differ much. Sugar control is imperative in diabetic LSRPN, and hence choice between IVIG and corticosteroids should be done appropriately *Infections*: It requires treatment with antibiotics and surgical drainage of abscess *Traumatic*: Cases of nerve disruption secondary to pelvic fractures and hip surgeries should be treated with supportive therapy *Neoplastic*: Benign tumours need observation. If deficits progress, then resection is considered with attention to preservation of neural integrity. Malignant infiltration should be treated with appropriate protocols under the guidance of an oncologist *Radiation*: No specific treatment exists for radiation plexopathy
Management of neuropathic pain	Neuropathic pain is often severe in cases of LSP and can cause severe disability. Early use of immunotherapy helps in resolution of pain. Antiepileptic or antidepressant medications such as pregabalin, gabapentin, amitriptyline and duloxetine can be helpful
Physical therapy	Because of marked weakness, physical therapy with orthosis plays an important role in management of LSP. Ankle foot orthosis and knee braces can be helpful to prevent falls and improve walking

Thaisetthawatkul and Dyck (2010), Mauermann et al. (2009), Khadilkar et al. (2015), Dyck and Thaisetthawatkul (2014), Chan et al. (2012) and Dyck and Windebank (2002)

32.8 Prognosis

Prognosis of LSP depends on the underlying aetiology. Diabetic and nondiabetic LSRPN are usually monophasic illnesses and most cases show improvement within 2 years of onset, but it can be incomplete. Prognosis is guarded for radiation, traumatic and neoplastic plexopathy, as these tend to lead to severe residual deficits.

32.9 Case Study

Clinical details: A 25-year-old lady presented with a 6 months history of gradually progressive pain in the left gluteal region radiating to left lower limb (LL). Pain was dull aching and particularly worsened during night time in supine position. She has also noticed paresthesias and burning sensation in the left foot and leg. Four months

before presentation, she has noticed progressive weakness and wasting of left leg to such an extent that she was not able to move her left foot in either direction. She had low-grade intermittent fever and weight loss of 6 kg as well. There was no history of aggravation of pain on bending or coughing, sensory/motor complains in the lower limb, bowel/bladder complains, complains in upper limbs, cranial nerve involvement, headache and vomiting or seizures. On examination, there was hypotonia in the left lower limb. There was weakness in the left lower limb, hip abductors and extensors were 4/5, knee flexion was 2/5 and there were no movements at ankle or toes. There was sensory loss over posterior aspect of thigh, leg and foot on left side. Ankle reflex was absent, while knee reflex was preserved. Right LL examination was completely normal.

Summary: This 25-year-old female had severely painful, gradually progressive, strictly unilateral severe motor-sensory deficit with background of low-grade fever and weight loss.

Discussion: As patient had severe, painful, strictly unilateral, severe sensorimotor deficits without bowel or bladder involvement, possibility of plexus lesions was much more likely than root lesion (Table 32.5). The pain had the red flag of increasing during the rest hours. Electrophysiology showed absent sural, superficial peroneal and saphenous SNAPs and severely attenuated tibial (abductor hallucis, gastrocnemius) and peroneal (extensor digitorum brevis, tibialis anterior) CMAPs on left side. NEE demonstrated active and chronic severe denervation in distribution of the left sciatic nerve and gluteal nerves and changes of mild denervation in left quadriceps but no spontaneous activity in paraspinal muscles. Electrophysiology confirmed lower LS plexus and nerve (sciatic and gluteal) involvement. MRI neurography was planned in order to evaluate the nature of lesion. MRI showed a large mass involving lower LS plexus, which exhibited variegated contrast enhancement and spared the LS roots (Fig. 32.3). USG-guided biopsy demonstrated round cell tumour which was confirmed as primitive neuroectodermal tumour (PNET). Thus, a clinical, electrophysiological and radiological approach helped to localise the lesion and yielded the cause.

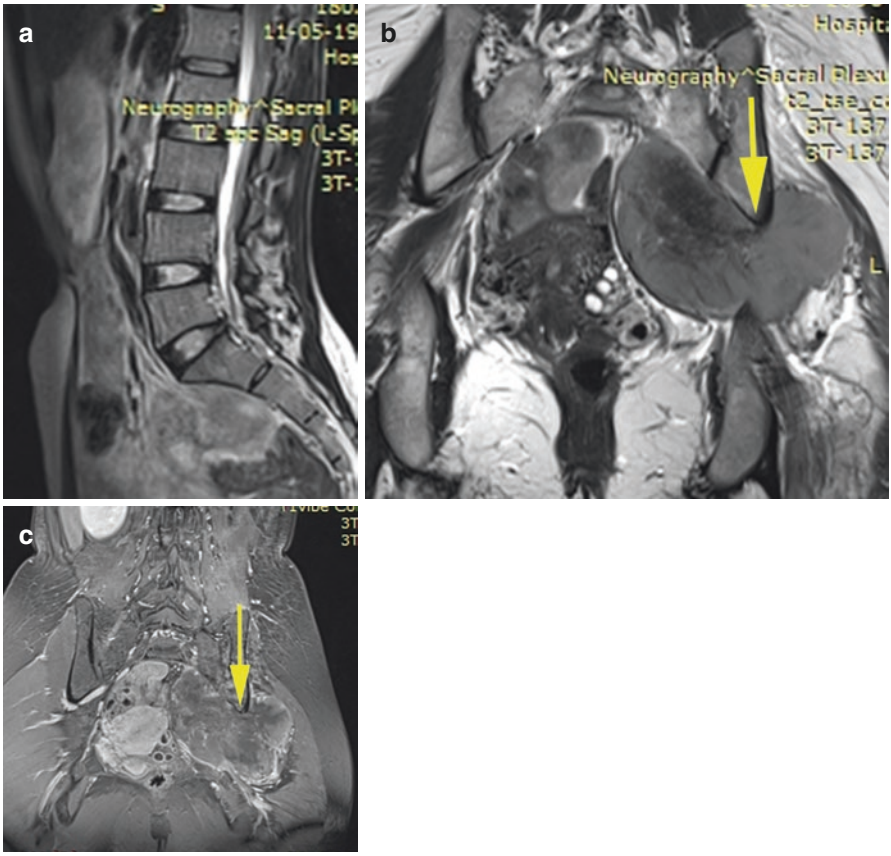

Fig. 32.3 (**a**) MRI LS spine shows no involvement of LS roots. (**b**) MRI T2 coronal images of LS plexus shows a large, hypointense mass affecting lower LS plexus and (**c**) post-contrast T1 coronal images show variable contrast enhancement of the mass

Key Points

When to suspect

- Unilateral sensorimotor deficits
- Often pain at onset
- Background of diabetes

How to diagnose

- SNAPs absent
- NEE showing changes in two nerves or branches of plexus
- MRI neurography or ultrasound of nerves
- Biopsy in selected cases

How to treat

- Guided by the aetiology

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Compressive Radiculopathies

33

33.1 Introduction

Compressive radiculopathy is a clinical condition resulting from compression of nerve roots. Cervical and lumbar segments are commonly affected by disc diseases which are common in current lifestyles. Other conditions like infiltrations, infections and neoplasms also result in radiculopathies and need to be identified and treated early. A knowledge of anatomical segmental supply helps localise the site clinically. MRI and electrophysiology are the key investigation for diagnosis. Conservative and definitive therapies need to be employed judiciously for best results.

33.2 Clinical Features

The clinical manifestations are broad and include pain, sensory deficits, motor deficits, diminished reflexes or any combination of the above. In compressive radiculopathy, sensory loss occurs in a dermatomal distribution and weakness in a myotomal distribution. Dermatomal sensory loss is less than expected because of extensive overlap in the innervations zones of spinal roots. As most muscles receive multisegment innervations, weakness in radiculopathy is also usually less than expected for a given myotome. Radicular pain may exacerbate with cough, sneeze or Valsalva manoeuvre. A history of cancer, unexplained weight loss, pain lasting longer than 1 month, pain unrelieved by bed rest, fever, focal spine tenderness, morning stiffness, improvement in pain with exercise and failure of conservative treatment are red flags which raise the suspicion of infiltrative processes. Table 33.1 summarises findings in various roots affected by compressive radiculopathies.

Conus medullaris and cauda equina regions have anatomical properties which lead to multiple root involvements. Multiple roots, including those for the sphincters, traverse this region and are compactly placed; hence, small lesions can lead to devastating deficits. As conus houses the sacral segments while cauda incorporates

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Table 33.1 Roots affected and deficits in common radiculopathies

Root	Sensory area	Motor supply	Reflex	Remarks
C5	Lateral arm	Levator scapulae, rhomboids, serratus anterior, supraspinatus, infraspinatus, deltoid, biceps, brachioradialis	Biceps, brachioradialis	
C6	Lateral forearm, lateral hand, first and second digit	Serratus anterior, biceps, pronator teres, flexor carpi radialis, brachioradialis, extensor carpi radialis longus, supinator, extensor carpi radialis brevis	Biceps, brachioradialis	Second most common; inverted radial reflex; finger flexor response
C7	Third and fourth digits	Serratus anterior, pectoralis major, latissimus dorsi, pronator teres, flexor carpi radialis, triceps, extensor carpi radialis longus, extensor carpi radialis brevis, extensor digitorum	Triceps	Most common; difficulty in opening the hand [Pseudomyotonia]
C8	Fifth digit, medial forearm and arm	Flexor digitorum superficialis, flexor pollicis longus, flexor digitorum profundus I to IV, pronator quadratus, abductor pollicis brevis, opponens pollicis, flexor pollicis brevis, all lumbricals, flexor carpi ulnaris, abductor digiti minimi, opponens digiti minimi, flexor digiti minimi, all interossei, adductor pollicis, extensor digiti minimi, extensor carpi ulnaris, abductor pollicis longus, extensor pollicis longus and brevis, extensor indicis	Finger flexor reflex	Horner syndrome
T1	Medial arm	Abductor pollicis brevis, opponens pollicis,, flexor pollicis brevis, all lumbricals and interossei, abductor digiti minimi, opponens digiti minimi, flexor digiti minimi, adductor pollicis, extensor digiti	Finger flexor reflex	Horner syndrome
L3	Lower anterior thigh, medial aspect of knee	Pectineus, iliopsoas, sartorius, quadriceps, thigh adductors	Patellar reflex	
L4	Medial leg	Quadriceps, sartorius, tibialis anterior	Patellar reflex	

Table 33.1 (continued)

Root	Sensory area	Motor supply	Reflex	Remarks
L5	Lateral leg, dorsomedial foot, large toe	Gluteus medius, gluteus minimus, tensor fasciae latae, semimembranosus, semitendinosus, tibialis posterior, tibialis anterior, peronei, flexor digitorum longus, extensor digitorum brevis, extensor hallucis longus, extensor digitorum longus	–	
S1	Little toe, lateral foot, sole	Gluteus maximus, biceps femoris, gastrocnemius, soleus, flexor hallucis longus, flexor digitorum longus, all small muscles of foot, extensor digitorum brevis	Achilles reflex	

Table 33.2 Comparison between conus medullaris and cauda equina lesions

	Conus medullaris	Cauda equina
Pain	Bilateral and symmetric Funicular and in pelvic area	Radicular distribution Radiating and in limbs
Sensory loss	Bilateral and symmetric Perianal and sacral areas affected	Unilateral and asymmetric Usually in distal lower limbs
Motor loss	Symmetric, less severe	Unilateral and symmetric, more severe
Bladder and bowel involvement	Marked	Not marked, absent or late
Reflexes	Only Achilles reflex absent	Both patellar and Achilles absent

the lumbar as well as sacral roots, the differences between the two conditions are primarily based on these anatomical boundaries. Table 33.2 summarises the differences between conus medullaris and cauda equina locations. In clinical practice, conus and cauda lesions can be seen together, and the differentiations mentioned below may not be strictly seen in a given clinical condition.

33.3 Investigations

MRI cervical spine or lumbosacral spine and electrophysiological studies are helpful in diagnosis by defining the anatomical involvement and hinting towards the nature of compression. Electrophysiology study helps in exact localisation prior to surgery.

33.4 Differential Diagnosis

Diagnosis	Key differentiating features
Cervical radiculopathy	
Myofascial pain	Put chin to chest and to either shoulder, each ear to shoulder and to hold the head in full extension – pain on the symptomatic side on putting the ipsilateral ear to the shoulder suggests radiculopathy, but increased pain on leaning or turning away from the symptomatic side suggests a myofascial origin. Changing pain sites, point tenderness is common
Bursitis capsulitis tendinitis	Passive movements also painful Point tenderness at inflamed sites
Carpal tunnel syndrome	Tinel sign Tingling numbness mainly distal to wrist but can radiate proximally
Brachial plexopathy	See chapter on brachial plexopathy
Lumbosacral radiculopathy	
Facetal arthropathy	Local pain, pain increasing on changing sides while lying down, extension and supine positions Better on walking and flexion
Musculoligamentous pain	Worse on walking, bending, stooping and minor movements Decreased by sitting or lying down
Spinal canal stenosis	Worse when standing Tingling numbness in lower limbs while walking (neurogenic claudication)
Restless leg syndrome	Unpleasant sensation in leg, especially during rest or period of inactivity, and improved with leg movements

33.5 Management

Nonoperative treatment of radiculopathy consists of a number of different modalities including immobilisation, physical therapy, manipulation, medication and epidural steroid injection (Rhee et al. 2007; Abdi et al. 2007). In the absence of myelopathy or significant muscle weakness, all patients should be treated conservatively for at least 6 weeks (Woods and Hilibrand 2015). Progressive neurological deficits warrant early surgical intervention.

33.6 Prognosis

Most compressive radiculopathies respond to conservative therapy with complete or largely complete recoveries. A minority necessitate surgical decompression.

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Leprosy

34

34.1 Introduction

Leprosy is a chronic mycobacterial infection of the skin and peripheral nervous system caused by *Mycobacterium leprae*. The characteristic clinical features are painless wounds, multiple mononeuropathies (MM), skin lesions and thickened nerves. The neuropathy of leprosy affects the temperature sense maximally; large sensory and motor fibres and deep tendon reflexes tend to be normal till late. Loss of proprioceptive sensations, patchy cranial neuropathies, generalised polyneuropathy and spinal cord involvement are uncommon but known to occur in patients with leprosy. Diagnosis is confirmed by demonstration of leprae bacilli in the skin or peripheral nerves using special stains. Electrophysiological and radiological investigations can be of help in localising the site of nerve biopsy, when skin lesions are absent. Immune-mediated reaction states can occur. Treatment consists of antibacterial medications and immunosuppressive agents. Although various strategies are expected to promote elimination of leprosy, it still remains one of the most common aetiologies of MM in few endemic areas of the world (Handbook of Clinical Neurology 2014).

34.2 Epidemiology

Leprosy is one of the oldest known diseases and has been known to affect humans for at least 4000 years. Leprosy is believed to have had its origin in early inhabitants of East Africa and spread worldwide with human migration and trade. In 1873, Norwegian physician Gerhard Armauer Hansen identified *M. leprae* as a cause of leprosy. Annual detection of new cases is on decline worldwide, but large areas of high endemicity such as Southeast Asia, South America, Africa, Eastern Pacific and Western Mediterranean regions still exist. Globally, annual detection of new cases has declined from 620,638 in 2002 to 219,075 in 2011. Rates of prevalence and new

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case detection are 1 case per 10,000 and 100,000 population all over the world. A total of 127,000 new cases were detected in 2013–2014. Rate of new case detection is 9.98 per 100,000 populations in India, which is ten times higher than the annual rate worldwide (Murthy et al. 2014; Lastória and Abreu 2014; Kumar 2015).

34.3 Clinical Features

The classical clinical presentation is a combination of hypopigmented, hypoaesthetic skin patches and neuropathy. Immunological reactions after starting antibacterial therapy can worsen nerve function and may cause systemic manifestations. Occurrence of pure neuritic type of leprosy with no apparent dermatological manifestations is uncommon and intriguing. As *M. Leprae* require cooler temperatures for growth, the skin and cranial and peripheral nerves at superficial location and the testis and anterior one third of the eye are affected, while vital internal organs are clinically unaffected. The clinical spectrum of leprosy is described in Table 34.1.

Clinical spectrum of leprosy is wide and ranges from isolated nerve or cutaneous involvement to extensive skin lesions and disabling neuropathy. This wide spectrum is embodied in Ridley–Jopling classification based on clinical, bacteriological and pathological features (Table 34.2).

To avoid complexity and simplify treatment strategies, WHO recommends classification of leprosy into paucibacillary (PB, less than or equal to five skin lesions) and multibacillary (MB, six or more skin lesions) (Pardillo et al. 2007; Handbook of Clinical Neurology 2014; and http://apps.who.int/medicinedocs/en/d/Jh2988e/4.html).

Table 34.1 Clinical spectrum of leprosy (Fig. 34.1)

Cutaneous features	Hypopigmented, hypoaesthetic patches occur over cooler parts of the body and in distribution of affected nerves These patches occur over the pinnae of ears, dorsomedial surface of forearm, dorsum of hands and feet, elbow, anterior knee, medial leg, nose, malar areas, central abdomen and buttocks The cutaneous involvement is patchy, and affected areas may be surrounded by certain areas with preserved sensations Warmer areas such as the palms, soles, inguinal folds, popliteal fossa, scalp, axilla and perineum are spared Patches in tuberculoid leprosy (TL) are hypoaesthetic and have elevated and erythematous margins and atrophic centre. There is loss of adnexal structures leading to hypopigmentation, loss of sweating and hair follicles Confluent skin lesions, leonine facies (deeply furrowed 'lumpy face' with prominent superciliary arches) and madarosis (loss of eyebrows and eyelashes) occur in lepromatous leprosy

Table 34.1 (continued)

Neuropathy	Neuropathy tends to predominantly affect small fibres (temperature > touch > pain), results in negative sensory symptoms (numbness, anhidrosis, anaesthesia and painless wounds) and produces patchy motor deficits in distribution of the affected nerve. Positive sensory symptoms such as paraesthesias (pins and needles), pains (allodynia and dysaesthesias) and hyperhidrosis are less common, and their occurrence often heralds the beginning of lepra reactions. Thickening of nerves is perhaps the most important clinical sign in leprosy. Tenderness of thickened nerves associated with beaded appearance strongly favours leprosy. Ulnar, superficial radial, posterior tibial, peroneal, greater auricular and supraorbital nerves are known to be thickened (Fig. 34.1). Sensory and motor Tinel's signs may be observed on tapping the affected nerves. Proximal muscles, deep tendon reflexes and large fibre sensations tend to be spared in most cases. In severe cases with pan sensory loss, there can be painless wounds, disabilities and deformities. Various patterns of nerve involvement are described below: **MM**: It is the most common pattern of peripheral nerve involvement, particularly in TL. Commonly affected nerves are sural, posterior tibial, ulnar, peroneal, median, superficial radial and the greater auricular. Sensory and motor affection within a single nerve is patchy as leprosy tends to affect small nerve twigs as they become superficial **Distal, small fibre, painful sensory polyneuropathy**: Few cases can have small fibre polyneuropathy similar to diabetes mellitus. Distal small fibre sensations are predominantly affected symmetrically. In some cases, there may be sensorimotor neuropathy with depressed tendon reflexes. It usually occurs in lepromatous leprosy **Ganglionitis and impaired large fibre impairment**: Uncommonly, leprosy can affect proximal segments. Involvement of dorsal root ganglia results in severe impairment of proprioception and thus leads to pseudoathetosis **Spinal cord involvement**: isolated case studies of spinal cord involvement in addition to dorsal root ganglia have been reported, but as yet, these are very few **Cranial neuropathy**: In a small proportion of leprosy patients, cranial nerves can be affected. Commonest are facial and trigeminal nerves, but 8th, 12th and other cranial nerves can get affected. Leprosy can lead to involvement of small twigs of cranial nerve fibres leading to patchy cranial neuropathy, e.g. patients may have isolated eye closure weakness with sparing of lower half of the face which is characteristic of leprous neuropathy
Immunological manifestations	Within 6 months of initiation of multidrug therapy, immunological phenomena can cause considerable worsening of nerve function and systemic features. They are of two types Type I reactions (reversal reactions): It is commonly seen in borderline leprosy, and it moves the disease towards tuberculoid pattern. It results due to increase in T-cell reactivity against mycobacterial antigens. Type II reactions (erythema nodosum leprosum): These are commonly seen with lepromatous leprosy. Frequent manifestations are skin nodules, neuritis, orchitis, lymphadenitis, arthritis and iritis

Khadilkar et al. (2007, 2008), Handbook of Clinical Neurology (2014), de Freitas et al. (2003), Khadilkar et al. (2015); Kumar et al. (2006), Madhusudanan (1999)

Table 34.2 Overview of Ridley–Jopling classification

Indeterminate leprosy (I)	The first type of skin lesions with hypopigmented spots
Tuberculoid leprosy (TT)	Hypopigmented hypoaesthetic patches with thickened nerves. Either go to BB stage or get cured. Low infective stage
Borderline tuberculoid leprosy (BT)	Small and numerous skin lesions
Borderline leprosy (BB)	Small irregular red lesions
Borderline lepromatous leprosy (BL)	Plaques, macules, nodules seen
Lepromatous leprosy (LL)	Multiple skin lesions, madarosis, deformities. High infective stage

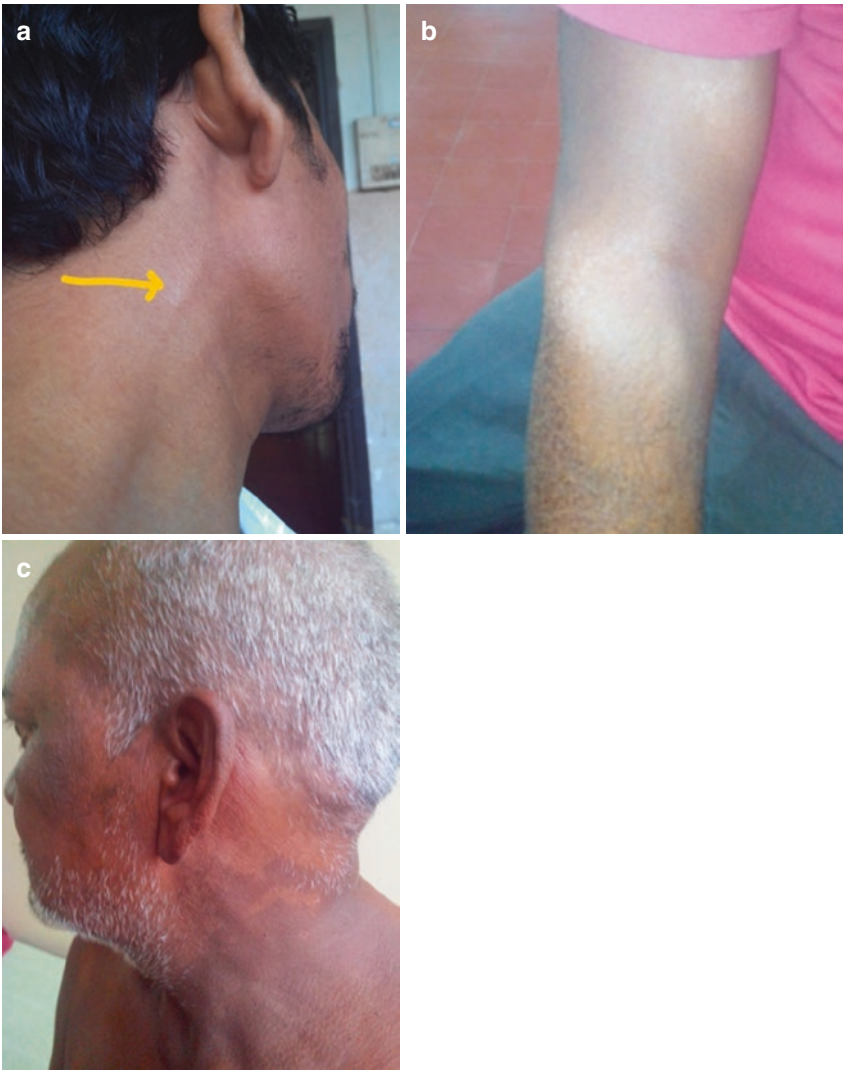

Fig. 34.1 (**a**) Thickened greater auricular nerve and (**b**) and (**c**) hypopigmented patches devoid of skin appendages in a patient with leprosy

34.4 Pathophysiology

M. leprae shows affinity to Schwann cells via laminin 2 and dystroglycan receptors. Density of Schwann cells surrounding small fibres is more than the large nerve fibres. Small fibres are abundantly found in superficial sensory nerves of the extremities. Hence, the initial damage is in these small nerve fibres. *M. leprae* requires temperature of 28–32 degrees for growth, which is lower than that of core body temperature. Hence, nerve twigs which are superficial and are placed in cooler locations, e.g. ulnar, common peroneal nerves etc., are affected early. *M. leprae* causes nerve damage by direct damage or by activation of inflammatory response. *M. leprae*-induced nerve damage is mediated via ErbB2 receptor tyrosine kinase signalling, which results in nerve demyelination (Rambukkana 2001; Tapinos et al. 2006; Wilder-Smith and van Brakel 2008; Madhusudanan 1999).

34.5 Investigations

When leprosy is suspected clinically, investigations are done to confirm the diagnosis and to localise the site of nerve biopsy. These investigations are summarised in Table 34.3.

Table 34.3 Investigations in clinically suspected leprosy (Fig. 34.2)

Electrophysiological tests	There is reduction in amplitude of sural, radial cutaneous, median and ulnar sensory nerve action potentials (SNAPs). There is a drop in compound muscle action potentials (CMAPs) and slowed motor conduction velocities across elbow segment of the ulnar nerve. When sural and radial cutaneous nerve SNAPs are unrecordable, these nerves can provide good yield on biopsy. Absence of sympathetic skin response (SSR) suggests impaired sudomotor function. Electrophysiology can also help to monitor toxicity of therapy, e.g. dapsone- or thalidomide-induced neuropathy
Radiological tests	High-frequency ultrasound (US): It can help to evaluate thickened nerves in leprosy. It also helps to detect skip lesions and nerve thickening at nonpalpable sites. Enlargement of nerves can be assessed more accurately with US than with clinical examination MRI: it can help to detect and confirm thickening of affected nerves and also help to assess fascicular architecture
Biopsy	Skin biopsy: Acid-fast bacilli can be detected on Fite Faraco staining of slit skin smear. It has a specificity of nearly 100% with 50% sensitivity. Histopathological examination shows presence of epithelioid granulomas and foamy macrophages. Immunohistochemistry and culture of *M. leprae* on mouse foot pad can be done to increase diagnostic yield Nerve biopsy: Biopsy yield of clinically affected nerve is higher, and sural or radial cutaneous nerves are usually chosen to confirm leprous neuropathy. In cases of mononeuropathy, fascicular biopsy of affected nerve can be helpful to reduce residual effects. Radiological tests can help to localise the site of biopsy in such cases. In lepromatous leprosy, macrophages and Schwann cells are filled with numerous acid-fast bacilli, while caseating granulomas with few or undetectable bacilli are seen in tuberculoid leprosy

(continued)

Table 34.3 (continued)

Serological tests	Many antibodies have been evaluated in leprosy, but the most widely studied of them is anti-PGL1 (phenolic glycolipid-1) antibody. It is helpful in detecting relapse and detecting subclinical infection. However, the role of these antibodies in diagnosis of leprosy is yet to be analysed

Handbook of Clinical Neurology (2014), Martinoli et al. (2000); International Leprosy Association Technical Forum (2002)

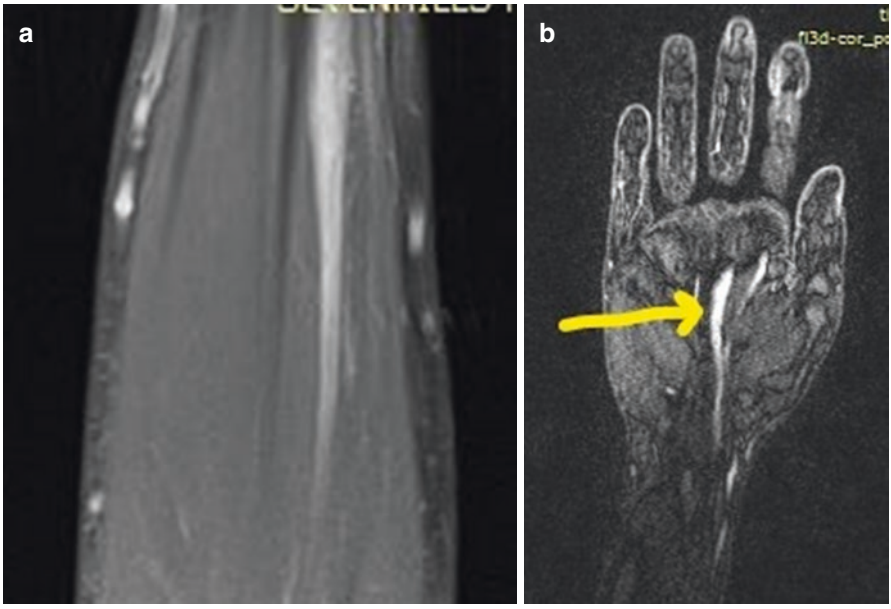

Fig. 34.2 Nodular thickening and contrast enhancement involving median nerve at the (**a**) forearm and (**b**) hand

34.6 Differential Diagnosis

All the characteristic features of leprosy may not be seen in all cases. Leprosy can present as small fibre neuropathy or mononeuritis multiplex or hypertrophic neuropathy or combination of these. Other diseases can mimic leprosy and need to be differentiated from leprosy (Table 34.4).

Table 34.4 Differential diagnosis of leprosy

Differential diagnosis of small fibre neuropathy	
Hereditary sensory autonomic neuropathy (HSAN)	Childhood onset; painless ulcers without any skin patches or nerve thickening; presence of features of autonomic dysfunction and evidence of generalised sensory neuropathy favour HSAN
Amyloidosis	Elderly onset; painful paraesthesias; distal > proximal; lower limb > upper limb; symmetrical small fibre > motor neuropathy; prominent autonomic features; uniform nerve thickening favours amyloidosis

Table 34.4 (continued)

Diabetes	Elderly onset; painful distal paraesthesias; distal symmetrical onset and glove and stocking pattern; presence of dysautonomic features and absence of nerve thickening favour diabetic neuropathy
Differential diagnosis of mononeuritis multiplex	
Vasculitic neuropathy	Pain is the hallmark of vasculitic neuropathy; associated systemic features like purpura, skin rashes, lung or kidney involvement; proximal muscle weakness in severe illness; characteristic features on nerve biopsy; absence of thickened nerves (Note: pain can be present in leprous neuropathy when in reaction state.)
Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)	Fourth decade onset; more common in females; onset in upper limbs; proximal and distal involvement; painful paraesthesias; depressed deep tendon reflexes; absence of skin patches; beaded thickening of nerves and tenderness; multifocal demyelination; elevated CSF proteins favour MADSAM
Hereditary neuropathy with liabilities to pressure palsies (HNPP)	Absence of skin patches; motor more than sensory involvement; nerve thickening can be present but absence of tenderness; absence of painless wounds; relapsing course with acute worsening; pes cavus; areflexia and multifocal demyelination suggest HNPP
Differential diagnosis of hypertrophic neuropathy	
Nerve thickening can be seen in hereditary sensorimotor neuropathy (HMSN), neurofibromatosis, Refsum's disease, chronic inflammatory demyelinating neuropathy (CIDP), amyloidosis and neoplastic infiltration. Unlike in these diseases, nerve thickening is nodular and tender in leprosy	

34.7 Management

Treatment approaches include medications and management of disabilities.

34.7.1 Medications

Both antibacterial and anti-inflammatory agents are useful. Antibacterial therapy is based on the WHO classification of leprosy. For single-lesion PB leprosy, single dose of rifampicin, ofloxacin and minocycline (ROM) may be considered. For other PB forms, monthly 600 mg rifampicin along with dapsone 100 mg daily should be given for 6 months. For MB leprosy, monthly supervised rifampicin 600 mg and clofazimine 300 mg with dapsone 100 mg and clofazimine 50 mg daily doses are recommended. Corticosteroids form the anti-inflammatory agents of choice and are known to improve the nerve function in 60–70% of patients with nerve involvement. Few randomised control trials (RCTs) have evaluated efficacy of steroids as compared to placebo. Few trials have demonstrated significant improvement of nerve function with steroids. Steroids can be given for 3–6 months' duration or more. Exact dose and duration of steroids are yet to be standardised. Further RCTs are needed to establish optimal corticosteroid regimens and evaluate efficacy of steroids

(Handbook of Clinical Neurology 2014; Van Veen et al. 2016; Rao and Suneetha 2016; Sahay et al. 2015). WHO recommends use of steroids for at least 12 weeks for type 2 lepra reactions. Another medication that has been used is thalidomide. Recently cyclosporine has been shown to be an effective alternative to steroids in type 1 lepra reactions (Lambert et al. 2016). Both these agents are currently considered when the response to corticosteroids is suboptimal.

34.7.2 Management of Disabilities

Due to eye closure weakness and decreased corneal sensations, corneal ulceration tends to occur. Eye patch should be applied during sleep to prevent corneal xerosis. Corneal ulceration should be treated with topical antibiotics. Neuropathy causes dryness, anaesthesia and muscle weakness. Dryness can lead to skin cracking and secondary infection. Patients should soak their hands and feet in water and apply petroleum jelly on their hands and feet. Ulcers should be treated with topical antibiotics and dressing. Orthotics and rehabilitation help to improve function secondary to muscle weakness (http://apps.who.int/medicinedocs/en/d/Jh2988e/4.html).

34.8 Prognosis

Leprous neuropathy can cause skin dryness, anaesthesia, increased risk of ulceration and muscle weakness. Severe illness can affect large fibre sensations. All these factors coupled with the chronicity of the disease can potentially lead to limb deformities. Early diagnosis and treatment are effective in preventing such complications of leprous neuropathy.

34.9 Case Study

Clinical details: A 50-year-old male presented with complains of gradually progressive numbness of both feet for two and a half years and of both hands for 2 years. He noticed swelling and redness of both feet after immersion in warm water. He developed difficulty in perceiving hot and cold sensations and burnt his fingers while holding a hot cup of tea, as he couldn't appreciate heat (Fig. 34.3). There was no history of systemic complaints (joint pain, oral ulcers, fever), burning pain or dysaesthesias, imbalance while walking or slipping of objects from hands without knowledge, weakness, bowel bladder involvement, presyncope, facial numbness or eye closure weakness. Patient has diabetes and hypertension, which was controlled with medications. He was born to nonconsanguineous parents and family history was not contributory. On examination, scars of burns were seen in fingers. A careful cutaneous search did not reveal any hypopigmented or hypoaesthetic patches, and there was no thickening or tenderness of nerves. On sensory examination, there was bilateral symmetrical, severe loss of pain, fine touch and temperature below elbows and knees.

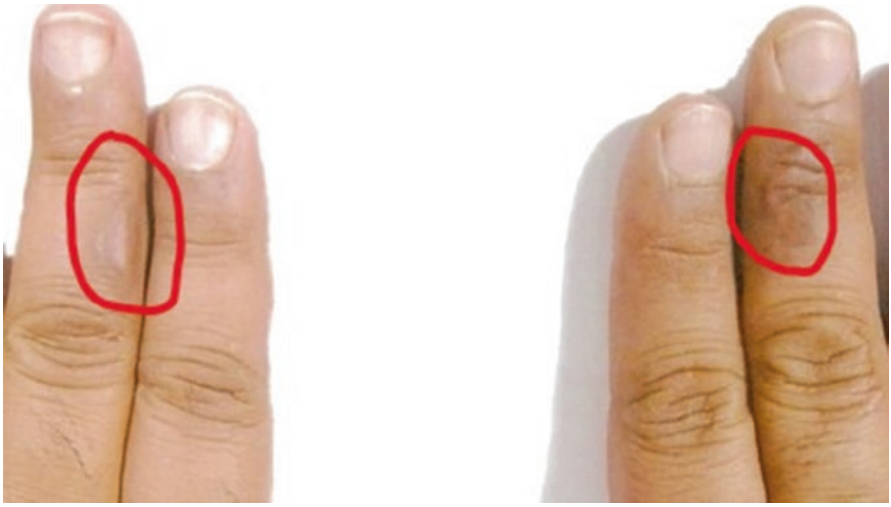

Fig. 34.3 Painless burn marks over fingers of both hands

Vibration sense was decreased below mid-tibial shin and was preserved in upper limbs. Deep tendon reflexes in lower limbs were depressed; position sense and motor examination were normal. Complete blood count, erythrocyte sedimentation rate, blood sugar, thyroid profile, toxic screening, HIV and HbsAg were normal. Cerebrospinal fluid examination was normal.

Summary: 50-year-old male presented with two-and-half-year history of progressive, severe, symmetric small fibre neuropathy affecting lower limbs more than upper limbs, generalised hyporeflexia and mild large fibre impairment in feet, without any autonomic dysfunction.

Discussion: the following possibilities were considered:

- Diabetic small fibre neuropathy was considered as patient has history of diabetes and small fibre involvement. But since upper limb involvement was prominent, sugar levels were controlled, and numbness rather than dysaesthesias at the onset made diabetic neuropathy less likely.
- Vasculitic neuropathy was less likely as it was not associated with pain or systemic complaints. Also, the neuropathy was symmetric and affected mainly the small fibres.
- Amyloid neuropathy can cause small fibre neuropathy but is painful, and autonomic involvement is prominent. There was no organ dysfunction nor family history.
- Despite the fact that neuropathy was symmetrical and hypopigmented patches and thickened nerves were absent, leprosy was still considered as patient had affection of temperature sense, enough to have burnt himself without knowledge.

Nerve conduction study showed generalised sensory more than motor peripheral neuropathy affecting feet and hands. However, soleus H-reflex was bilaterally normal which pointed in a way to confluent mononeuritis multiplex. Nerve biopsy was done. The nerve was extensively affected with granulomatous inflammation and cicatrisation (Fig. 34.4), and the Fite Faraco staining demonstrated lepra bacilli. Thus, the diagnosis of pure neuritic leprosy was confirmed. Pure neuritic leprosy can pose diagnostic difficulties, and the diagnosis needs to be kept in mind.

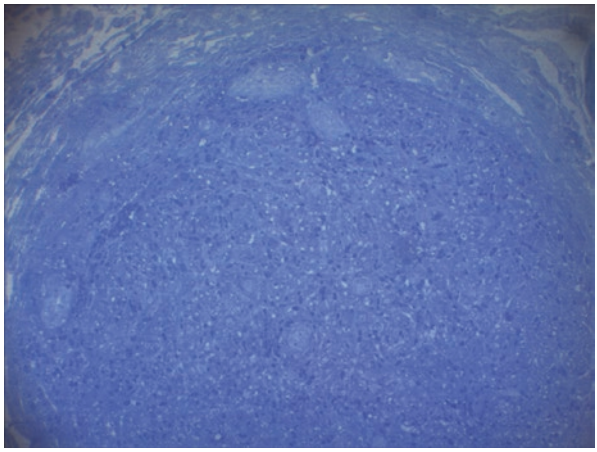

Fig. 34.4 Extensive fibrosis and granulomatous inflammation of the nerve

Key Points

When to suspect

- Sensory mononeuritis multiplex with thickened nerves
- Non-healing ulcers
- Anaesthetic skin patches
- Uncommonly pansensory neuropathy, leprous ganglionitis and pure neuritic leprosy

How to diagnose

- Electrophysiology confirming mononeuritis multiplex
- MRI neurography or ultrasound of nerves
- Skin or nerve biopsy with special stains

How to treat

- Dapsone, clofazimine, rifampicin
- Steroids for few weeks to few months
- Thalidomide in selected patients

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Hereditary Liability to Pressure Palsies

35

35.1 Introduction

HNPP is inherited in an autosomal dominant pattern and is characterised by recurrent mononeuropathies which can be precipitated by minor trauma or compression. Although acute mononeuropathies are common presentations, HNPP can uncommonly lead to progressive mononeuropathies and generalised neuropathy. Majority of the cases are caused by a 1.5 Mb heterozygous deletion at 17p11.2–12, while point mutations are extremely rare. Electrophysiological and histopathological features provide important clues, but genetic studies are now diagnostic for HNPP.

35.2 Epidemiology

The prevalence of HNPP is unknown; it is estimated at two to five cases per 100,000 populations. As all cases are not reported or registered, the actual prevalence is underestimated and may be higher (Bird 2014).

35.3 Clinical Features

HNPP presents in between 19 and 26 years of age [range 2–64 years]. Episodic, recurrent, acute-onset, asymmetrical, sensory motor weakness in nerve distribution is key feature. Usually weakness is painless and either mild and transient or persistent. Some individuals experience transient sensory phenomena without weakness. Mild trauma, compression, repeated local exercise and stretching are common prodromes. Sometimes weakness is noticed on awakening or after prolonged surgery. As trivial trauma can precipitate neuropathy, history of actual physical compression of the nerve may or may not be present. Commonly involved nerves are fibular nerve at the fibular neck, ulnar nerve at the elbow, the brachial plexus, radial nerve

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at the spiral groove and median nerves in the carpal tunnel. Reflexes are normal in 62%. Cramps and tremor may be associated features. Occasional patients have skeletal deformities like pes cavus and scoliosis. Commonly involved cranial nerves are trigeminal, facial, auditory, recurrent laryngeal and hypoglossal.

Various presentations of HNPP: multiple mononeuropathies, progressive mononeuropathies, generalised weakness and cramps, transient positionally induced sensory symptoms, chronic ulnar neuropathy, carpal tunnel syndrome, chronic sensory polyneuropathy, Guillain–Barré like, CIDP like, CMT like and motor brachial paralysis (Luigetti et al. 2014; Mouton et al. 1999; Korn-Lubetzki et al. 2002; Kumar et al. 2002). About 15% of mutation carriers remain asymptomatic.

35.4 Pathophysiology

PMP22 is tetra-span membrane protein primarily expressed in myelinating Schwann cells. Heterozygous deletion of the PMP22 gene (one copy) causes HNPP (Chance et al. 1993). Focal weakness and sensory loss related to mechanical stress induced failure of action potential propagation (Bai et al. 2010).

35.5 Investigations

35.5.1 Electrodiagnostic Tests

The presence of focal demyelination at one or more entrapment sites, e.g. median nerve at the wrist, ulnar nerve at the elbow and peroneal nerve at the head of fibula, is characteristic of HNPP. Such conduction slowing across entrapment sites can be detected in asymptomatic nerves. In addition to conduction slowing across entrapment sites, motor and sensory conduction slowing can be seen even at noncompression sites (Andersson et al. 2000). Manganelli et al. compared electrophysiological involvement in males and females and concluded that higher disease expression may increase the chance to detect the disease in males and, thereby, to underestimate the HNPP diagnosis in females (Manganelli et al. 2013).

35.5.2 Nerve Biopsy

Nerve biopsy demonstrates focal areas of folded myelin sheath known as tomacula. It is formed by overfolding of multiple layers in the myelin sheath. The folding is predominantly concentric around the axonal axis in HNPP. Tomacula are not unique to HNPP and have been found in anti-MAG neuropathy, CMT1B, CIDP and Tangier's disease. The frequency of occurrence of tomacula and its characteristic in these diseases are different (Madrid and Bradley 1975). As age progresses, there may be evidence of irreversible axonal damage at entrapment sites in motor nerves

in patients with HNPP. Sensory nerves tend to develop more profound axonal degeneration as compared to motor nerves. Unlike CMT1A, both ageing and persistent compression trigger axonal damage (Koike et al. 2005).

35.5.3 MRI

Cerebral white matter changes especially in frontal lobe are noted in conventional MRI and DTI scan (Wang et al. 2015).

35.5.4 Genetic Study

Genetic studies show a 1.5-megabase deletion of chromosome 17p11.2–12 that includes the PMP22 gene most of the patients with HNPP. It is intriguing that duplication of same gene is found in CMT1A. Frameshift or nonsense mutations in PMP22 gene can be seen in remaining cases but are very uncommon (Lenssen 1998 and van de Wetering 2002). The presence of family history of neuropathy in a patient with one or more episode of mononeuropathy makes a strong case for genetic testing. However, some experts recommend genetic testing for HNPP even in absence of positive family history (Bird 2014). The presence of features of generalised polyneuropathy, e.g. pes cavus and hyporeflexia in a patient with episode of mononeuropathy, should raise suspicion of HNPP and requires genetic testing for it.

35.6 Differential Diagnosis

As HNPP commonly presents with episodes of mononeuropathies, diagnosis is often straightforward. In cases of progressive mononeuropathies, presence of generalised neuropathy or multifocal involvement on electrophysiology, diagnosis of HNPP becomes challenging, particularly in absence of recurrent deficits and negative family history. Differential diagnosis of HNPP has been summarised in Table 35.1.

Table 35.1 Differential diagnosis of HNPP with their key differentiating features

Differential diagnosis	Key distinguishing features
Compressive neuropathies	Presence of pain, positive sensory complains, localised nerve thickening and tenderness favour compressive neuropathies
Charcot–Marie–Tooth (CMT) disease	Presence of symmetrical distal weakness and wasting, absence of episodes of mononeuropathies and generalised conduction slowing on electrophysiology favour CMT. Frequency of pes cavus and foot deformities is more common in CMT than in HNPP

Differentials of multifocal neuropathies have been discussed in chapter on leprosy in the section of differential diagnosis

35.7 Management

Management of HNPP consists of treatment of pressure palsies and measures to prevent nerve injuries. During acute stage of pressure palsy, bracing and rehabilitation help to mitigate deficits in many patients. The use of bracing may be prolonged if there are residual deficits. Corticosteroids can help to improve deficits particularly in protracted and incomplete course of recovery, but routine use of steroids is not recommended (Heng et al. 2012). After the resolution of pressure palsy and confirmation of diagnosis of HNPP, preventing nerve injury becomes the mainstay of treatment. Patient education is of prime importance to avoid pressure damage. Certain activities such as sitting with legs crossed, repetitive movements at the wrist and striving for excessive weight loss make patients prone to pressure palsies. Hence, such activities should be avoided. Preventive pads at pressure points like the elbow and knee can be helpful. Certain toxins or medications are known to worsen neurodeficits in patients with pre-existing hereditary neuropathies and, hence, should be avoided (Weimer and Podwall 2006). Rarely, surgical decompression is required. Utility of surgical decompression in patients with HNPP and median neuropathy at the wrist have been highlighted in a case report (Earle and Zochodne 2013). However, surgical therapy and the use of steroids are controversial and are not routinely included in management of HNPP.

Measures to target genetic abnormalities in HNPP have been studied. Decrease in PMP22 gene is the prime genetic defect in HNPP, and various therapies have been proposed. PMP22 copies can be increased either by stimulation of endogenous PMP22 or by introducing another copy of PMP22 into the peripheral nerve by gene therapy. Although these therapies are in experimental phase, care has to be taken that increase in PMP22 above certain level can lead to CMT1A.

35.8 Prognosis

Recovery time is in days to months. Complete recovery is achieved in 50%, and severe long-term motor deficit presents in 9% of cases. HNPP patient may carry a high risk for certain surgical procedures not expected to cause neurological deficits in normal patients (Kramer et al. 2016). Genetic counselling (Bird 2014) has been well lined out by Bird and colleagues as applicable to parents, sibs, offsprings and other family members of a proband.

35.9 Case Study

Clinical details: A 15-year-old boy was admitted with the complaints of acute-onset distal weakness of the right lower limb, which was noticed as he got up from his sleep. He had difficulty in clearing the right foot off ground. He also noticed decreased sensation over lateral aspect of the right leg and dorsum of foot. He had been sitting cross-legged, studying till late night. There were no complaints pertaining to the

other limbs, no bowel, bladder changes, low backache or radicular pain. Weakness remained static. He had past history of two episodes of right shoulder weakness, which had recovered completely within few days without any treatment. Both these events were preceded by intensive sporting activities. There was no family history of similar complaints. On examination, there was sensory motor deficit in the distribution of right peroneal nerve. Two striking features were presence of pes cavus and absence of all deep tendon reflexes.

Summary: A 15-year-old boy presented with acute-onset peroneal neuropathy, pes cavus and generalised hyporeflexia on background history of recurrent neurological deficits.

Discussion: Presence of pes cavus and absence of DTRs in a case of acute peroneal neuropathy indicated the presence of an underlying chronic process. On nerve conduction studies, there was presence of conduction slowing across the head of fibula along common peroneal nerve. In addition, there was conduction slowing across other compression sites, e.g. median nerve at the wrist and ulnar nerve at the elbow. He also had conduction slowing along sensory nerves. Conduction slowing at multiple sites and past history of recurrent neurological deficits (brachial plexopathy) prompted the diagnosis of HNPP. A heterogeneous deletion was documented in the PMP22 gene.

Clues to HNPP in a patient presenting with acute mononeuropathy/plexopathy are:

- History of neurodeficit occurring after abnormal posture in index case/family
- Pes cavus
- Hyporeflexia
- Conduction slowing across compressive but clinically unaffected sites

Key Points

When to suspect

- Recurrent reversing mononeuropathies
- familial

How to investigate

- Electrophysiology
- PMP 22 gene

How to treat

- Conservative measures
- Avoid activities which stretch or trap nerves
- Counselling

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Part VII

Symmetric Sensory Motor Weakness

Guillain–Barré Syndrome

36

36.1 Introduction

GBS is an umbrella term describing a heterogeneous group of related disorders. Common pathogenesis of these disorders is mirrored by several shared clinical features, including history of antecedent infection, monophasic disease course and symmetrical cranial or limb weakness. In the last hundred years, some landmark observations have been made in the understanding and therapy of GBS, and they are listed in Table 36.1.

36.2 Epidemiology

Most studies that estimate incidence rates of GBS have been done in Europe and North America and showed a similar range of 0.8–1.9 (median 1.1) cases per 100,000 people per year (Sejvar et al. 2011a, b). Seasonal fluctuations, presumably related to variations in infectious antecedents, have been reported, but these observations are rarely statistically significant (Webb et al. 2015).

36.3 Clinical Features

36.3.1 Antecedent Events

Antecedent upper respiratory or gastrointestinal infective symptoms are present in over 90% of patients who develop GBS (Koga et al. 2001). *Campylobacter jejuni*, the most common cause of acute bacterial gastroenteritis, is consistently identified as the most frequent antecedent infection, occurring in up to 30% of patients (Poropatich et al. 2010). However, only 1 in 1000 patients with *C. jejuni* infection develops GBS (Allos 1997). The median time interval between onset of diarrhoea

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Table 36.1 Landmark observations in GBS

1916	Guillain, Barré and Strohl first time recognised two patients who developed acute areflexic paralysis in association with raised CSF protein without increased cell content (Guillain et al. 1916)
1938	Guillain had recognised various forms of GBS and proposed a clinical classification that took into account four presentations: the lower form, the spinal and midbrain form, the midbrain form and polyradiculoneuropathy with impaired mentation (Guillain 1938)
1956	Miller Fisher described three patients with 'an unusual variant of acute idiopathic polyneuritis [syndrome of ophthalmoplegia, ataxia and areflexia' which bore resemblance to the midbrain form proposed by Guillain. The Miller Fisher syndrome (MFS) (Fisher 1956)
1957	Bickerstaff described eight patients who presented with ophthalmoplegia, ataxia and hypersomnolence, similar to yet distinct from GBS polyradiculoneuropathy with impaired mentation (Bickerstaff 1957)
1978	Clinical diagnostic criteria for GBS were introduced following an increase in incidence after swine flu vaccination program (Asbury et al. 1978)
1990	Diagnostic criteria for pure motor GBS, pure sensory GBS, MFS, several localised subtypes of GBS and pure pandysautonomia (Asbury and Cornblath 1990)
2001	Classification criteria published by a GBS consensus group based in the Netherlands described several subtypes of GBS (Van der Meché et al. 2001)
2011	Criteria outlined by the Brighton collaboration GBS working group have used nerve conduction studies to identify patients with vaccination-related GBS or MFS (Sejvar et al. 2011a, b)
2014	The GBS classification group present clinical criteria to diagnose GBS and all its variants using a simple yet all-inclusive classification system (Wakerley et al. 2014)

and development of neurological symptoms is 10 days but may be as short as 3 days or as long as 6 weeks (Takahashi et al. 2005). Several other bacterial and viral infections are associated with the development of GBS. These include *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Cytomegalovirus*, Epstein–Barr virus and varicella zoster virus. Some of the remaining patients with no antecedent infectious symptoms may still be harbouring asymptomatic infection as half of the patients with *C. jejuni* do not develop gastrointestinal symptoms. Non-infective associations have also been reported (Wakerley and Yuki 2013). These include parenteral gangliosides for treating peripheral neuropathy and various vaccines (e.g. H1N1 influenza vaccine), which have the potential to induce molecular mimicry. Other associations include autoimmune diseases (e.g. systemic lupus erythematosus), immunosuppressive drugs (e.g. anti-TNF-α therapy) and surgery, probably reflecting the increased susceptibility to known infective triggers, some of which are asymptomatic.

36.3.2 Classical GBS

In most GBS patients, the onset of neurological symptoms is with distal paraesthesia rather than weakness. Weakness follows and rapidly becomes the dominant

symptom. It is often ascending and can involve respiratory muscles and cranial nerves. Many patients with GBS also report back pain, probably relating to inflammation of nerve roots (Wakerley and Yuki 2015). The time interval between onset of neurological symptoms and nadir ranges between 12 h and 28 days and is usually followed by subsequent clinical plateau or improvement (Sejvar et al. 2011a, b). Most patients reach their lowest point of weakness within a week or so, and progression beyond 2 weeks is uncommon. The key examination finding in patients with GBS-related disorders is relatively symmetric weakness, although some patients do develop asymmetric and rarely unilateral weakness. Classic GBS (tetraparesis) can be diagnosed in patients presenting with bilateral flaccid, areflexic limb weakness and is highly likely when there is also facial weakness (Ropper 1992). Up to 10% of patients have normal or exaggerated reflexes. The exact localisation and mechanism which underpin hyperreflexia in GBS remain unknown, but one theory is that anti-ganglioside antibodies may cross the blood–brain barrier and disrupt intramedullary interneurons (Yuki et al. 2012). Some patients with features otherwise typical of GBS also display 'extensor plantar responses and ill-defined sensory levels', indicating possible CNS involvement (Asbury and Cornblath 1990). Patients might have signs or symptoms of autonomic dysfunction like cardiac arrhythmia, excessive sweating, blood pressure instability or ileus any time during illness (Van den Berg et al. 2014a, b).

GBS can be difficult to diagnose in children, especially preschool children, because they may not be able to describe their complaints well and neurological examination is more challenging. Refusal to walk and pain in the legs are the most frequent presenting symptoms (65%), while older children present with more classic symptoms of weakness and paraesthesias. The preschool children are often initially misdiagnosed with myopathy, tonsillitis, meningitis, rheumatoid disorders, coxitis or discitis (Roodbol et al. 2011).

36.3.3 GBS Subtypes

Following subtypes of GBS have been described (Table 36.2).

Table 36.2 Subtypes of GBS with characteristic features

Subtype	Key distinguishing features
Pure motor form	No sensory symptoms or signs Can be axonal or demyelinating
Pure sensory form	No motor weakness Well known but does not meet the diagnostic criteria of GBS (Yang et al. 2014)
Miller Fisher syndrome	Ophthalmoplegia, ataxia, areflexia
Miller Fisher–Guillain–Barré overlap syndrome	Weakness in addition to the above triad

(continued)

Table 36.2 (continued)

Subtype	Key distinguishing features
Pharyngocervicobrachial (PCB) variant Forme fruste: acute isolated pharyngeal or bulbar weakness	Oropharyngeal, neck and arm weakness associated with areflexia and some sensory changes (Wakerley and Yuki 2014); sensory impairment was not included in the original description (Ropper 1986). Lower limb weakness is variable and mild
Paraparetic variant	Weakness restricted to lower limbs with subtle reflex or sensory changes in the upper limbs (Van den Berg et al. 2014a, b)
Bifacial variant with paraesthesias	Paraesthesias in addition to facial weakness separate this from other causes of bifacial weakness (Susuki et al. 2009)
Acute pandysautonomia	Combined sympathetic and parasympathetic failure without somatic sensory or motor involvement. Areflexia is common Half of the patients have autoantibodies to ganglionic acetylcholine receptors (Koike et al. 2013)

36.3.4 Red Flags for Diagnosis

Fever at onset, severe sensory signs with limited weakness at onset, persistent bowel or bladder dysfunction, bowel or bladder dysfunction at onset, severe pulmonary dysfunction with limited weakness at onset, sharp sensory level, marked persistent asymmetry of weakness.

36.4 Pathophysiology

GBS is usually preceded by infection or other immune stimulation that induces an aberrant autoimmune response targeting peripheral nerves and their spinal roots. Molecular mimicry between microbial and nerve antigens is clearly a major driving force behind the development of the disorder, at least in the case of *C. jejuni* infection. However, the interplay between microbial and host factors that dictates if and how the immune response is shifted towards unwanted autoreactivity is still not well understood. Furthermore, genetic and environmental factors that affect an individual's susceptibility to develop the disease are unknown (Willison et al. 2016).

36.5 Investigations

36.5.1 Electrophysiological Study

GBS is a clinically diagnosed disorder, but nerve conduction studies (NCS) can help to support the diagnosis, to differentiate between axonal and demyelinating subtypes and hence to help prognosis. Nerve conduction abnormalities are most

pronounced 2 weeks after start of weakness. NCS findings can be normal especially early in the course of disease. Abnormalities of H reflexes and F responses are most frequently noted in early AIDP. Additionally, upper limb sensory abnormalities with spared sural responses, distal temporal dispersion, prolonged or absent blink reflexes and A waves were often present in the acute stage of AIDP when classic diagnostic criteria of AIDP are not satisfied (Vucic et al. 2004). To increase the diagnostic yield, at least four motor nerves, three sensory nerves, F waves and H reflexes should be examined. NCS enable clinicians to divide GBS into acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy or acute motor and sensory axonal neuropathy. NCS in patients with acute inflammatory demyelinating polyneuropathy show features of demyelination, including prolonged distal motor latency, reduced nerve conduction velocity, prolonged F-wave latency, increased temporal dispersion and conduction blocks (Fig. 36.1). Features of axonal GBS (acute motor axonal neuropathy or acute motor and sensory axonal neuropathy) are decreased motor, sensory amplitudes or both. Some patients turn out to have transient conduction blocks or slowing that rapidly recovers during the course of the disease, so-called reversible conduction failure. This transient feature might initially suggest acute inflammatory demyelinating polyneuropathy instead of acute motor axonal neuropathy and emphasises the fact that serial NCS over weeks are needed to reliably distinguish between these two forms of GBS. Transient blocks are probably caused by impaired conduction at the node of Ranvier, because of the effects of anti-ganglioside antibodies in those cases in which they are found (Kokubun et al. 2013). A substantial proportion of acutely diagnosed patients with GBS cannot be classified into a category, either because the tractable nerves (i.e. the upper and lower limb nerves that can be readily accessed by surface electrodes used in clinical electrophysiology) are so severely affected that they are inexcitable or are physiologically normal; both states are uninformative for classification as acute motor axonal neuropathy or acute inflammatory demyelinating polyneuropathy. Furthermore, electrophysiological recordings can change during the clinical course and yield an acute inflammatory demyelinating polyneuropathy pattern early on and an acute motor axonal neuropathy pattern later (reversible conduction block) (Umapathi et al. 2012). NCS might also have prognostic value because patients with features of demyelination more often need mechanical ventilation and low compound muscle action potentials (CMAPs) are the most consistent findings predictive of poor outcome. Patients diagnosed with acute motor axonal neuropathy can either improve very slowly and incompletely or recover rapidly, probably because of restoration of transient conduction blocks. Pharyngeal–cervical–brachial weakness and paraparetic GBS are axonal form, whereas bifacial weakness with paraesthesias is demyelinating in nature (Arai et al. 2003; Nagashima et al. 2013; Susuki et al. 2009). Additional studies are needed to further establish the electrophysiological criteria for GBS and its subgroups and to precisely delineate the relation between these conduction blocks, the presence of anti-ganglioside antibodies, the effect of treatment and outcome (Uncini et al. 2015).

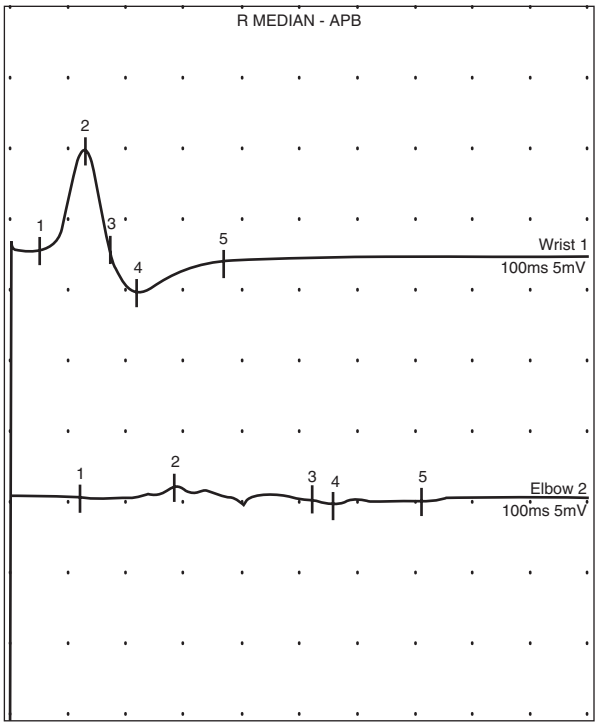

Fig. 36.1 Temporal dispersion and partial conduction block in AIDP (Courtesy: Dr. Khushnuma Mansukhani, Bombay Hospital, Mumbai)

36.5.2 CSF Study

Typically, cerebrospinal fluid (CSF) shows albuminocytological dissociation (high protein, normal cell count). In one large series, CSF protein was raised in 49% of patients on day 1 and 88% after 2 weeks. Fifteen percent had a mild pleocytosis (5–50 cells/mL (≤5)), but none had more than 50 cells/mL (Fokke et al. 2014).

36.5.3 Antibodies

Anti-ganglioside antibody testing is useful, but obtaining results takes time and, therefore, should not be relied on for diagnosis. GT1a is more densely expressed than GQ1b in human glossopharyngeal and vagal nerves. Patients with pharyngeal–cervical–brachial weakness often carry anti-GT1a IgG antibodies (Koga et al. 2002; Nagashima et al. 2007) (Table 36.3).

Table 36.3 Differential diagnosis of GBS

1. Viruses targeting anterior horn cells or motor neurons	
Poliomyelitis	It affects unvaccinated individuals, especially those with recent travel to endemic regions Most patients infected with polio remain asymptomatic, but 0.1%–1.0% develop paralysis Typically, there is a prodromal flu-like illness, with fever, neck stiffness and significant myalgia Rapidly progressive, often asymmetric paralysis, affecting proximal more than distal muscles, develops within 48 h in the absence of sensory deficit CSF examination shows active lymphocytic pleocytosis, early in the course.
Non-polio enterovirus (enterovirus 71)	Typically, a 1–2 week prodromal illness of diarrhoea, lethargy, irritability and nuchal rigidity is followed by acute flaccid paraparesis and other neurological symptoms in up to 20% of individuals. The mortality is high
Rabies virus	Rabies virus may cause acute flaccid paraparesis 1–2 months after initial exposure. Early symptoms include behavioural changes and autonomic instability, followed by ascending paralysis associated with sphincter involvement and sensory disturbance
HIV and opportunistic infections	Direct involvement of the spinal cord, nerve roots and peripheral nerves may occur in HIV or AIDS, but more often acute flaccid paraparesis is caused by the effects of opportunistic infections. These include cytomegalovirus, Epstein–Barr virus, varicella zoster virus and herpes simplex virus, which may also trigger acute motor axonal neuropathy. Cytomegalovirus and, less commonly, herpes simplex virus 2 or varicella zoster virus also cause polyradiculoneuropathy, especially if the patient is immunocompromised. Typically, there is ascending leg weakness, perineal paraesthesia, leg pain and variable bladder involvement. CSF usually shows increased polymorphs and protein with reduced glucose. Neurophysiologically, there is evidence of axonal neuropathy. Clinicians should also consider other infections, including syphilis, toxoplasmosis, giardiasis and tuberculosis. Patients with AIDS with cachexia may develop rapidly progressive weakness due to profound B12 deficiency
2. Acute transverse myelitis	Acute transverse myelitis may cause acute flaccid paraparesis, usually with radiological evidence of spinal cord involvement. Initial spinal shock is followed by acute flaccid paraparesis associated with bladder disturbance and a sensory level. Often patients present with back pain
Spinal cord injury	Spinal cord injury can usually be elicited from the history, and one should always ask about recent falls Epidural abscess or haematoma may cause acute spinal cord compression and is usually associated with focal pain and can be shown radiologically. Anterior spinal artery occlusion may cause abrupt onset of acute flaccid paraparesis and should always be considered postoperatively if there has been cardiothoracic surgery requiring aortic clamping

(continued)

Table 36.3 (continued)

3. Acute peripheral neuropathies	
Acute CIDP	If there is deterioration after 8 weeks from onset or more than three further deteriorations during disease course
Porphyric neuropathy	The onset can be acute and progression to nadir occurs in 4 weeks. CSF also shows albuminocytological dissociation, and nerve conduction studies show an axonal-type neuropathy. In half the cases, the weakness starts in the upper limbs and may therefore be confused with the pharyngocervicobrachial variant. Invariably, patients report severe abdominal pain and show psychiatric symptoms or have seizures before developing porphyric neuropathy. The diagnosis relies upon showing urinary porphyrins under ultraviolet light or following exposure to oxygen.
Tick paralysis	A flu-like prodrome lasting 5–10 days may be followed by rapidly progressive symmetric ascending flaccid paralysis over 2–6 days. Usually endemic
Lyme disease	Painful, often asymmetric polyradiculoneuropathy may occur several months after initial tick bite or after a characteristic erythema migrans rash. Isolated or bilateral facial weakness has also been reported. CSF shows raised lymphocytes and protein, and there is serological evidence of Lyme disease
Consumption of toxins or poisons (e.g. puffer fish poisoning (tetrodotoxin), lead, thallium, arsenic)	Heavy metal neuropathies are associated with skin and epithelial changes and features like alopecia in thallium, erythromelalgia in mercury, hyperkeratosis in arsenic toxicity
4. NM junction	
Autoimmune diseases (e.g. myasthenia gravis or Lambert–Eaton myasthenic syndrome), exposure to certain toxins (e.g. botulinum toxin), consumption of various plants (e.g. hemlock) or indeed animal bites (e.g. cobra or krait)	In most cases, rapidly progressive weakness in absence of sensory disturbance Muscle fatigability
5. Muscle disease	
Acute myositis	Acute myositis may develop following certain viral infections (e.g. influenza A) and is associated with variable degree of rhabdomyolysis. Typically, weakness begins within 2 weeks of the start of flu-like symptoms. Patients often look unwell and report myalgia and fever. On examination, the muscles are tender to touch and sometimes swollen, while sensation is normal. Serum creatine kinase is greatly elevated (often >10,000 U/L), and liver transaminases are also deranged. Urine dipstick is positive for blood, but there are no red blood cells on microscopy
Acute hypokalaemic periodic paralysis	Autosomal dominant. The paralysis often follows a high-carbohydrate meal or a prolonged period of exertion
Thyrotoxic periodic paralysis	Triggered by excess endogenous or exogenous thyroid hormones

Table 36.3 (continued)

6. Critical illness	
Critical illness myopathy	The intensive care unit patients who develop generalised weakness or are having difficulty weaning from mechanical ventilation. Although GBS may develop in this setting, neuromuscular weakness related to critical illness should always be considered first. Clinical assessment may be difficult as patients are often encephalopathic. Those receiving high-dose intravenous glucocorticoids (e.g. for status asthmaticus) are at particular risk of developing critical illness myopathy, which typically affects proximal more than distal muscles and starts several days after treatment initiation. There is sometimes facial weakness, although the ocular muscles are usually spared. The serum creatine kinase is raised, and nerve conduction studies may show slight motor nerve abnormalities
Critical illness neuropathy	Patients with severe sepsis may develop critical illness neuropathy, which has a worse prognosis. Weakness is often more distal and associated with sensory disturbance. Facial weakness is less common. The serum creatine kinase in these patients is usually normal, and nerve conduction studies show a diffuse sensorimotor axonal polyneuropathy
	These should be differentiated from cachectic myopathy, which may develop in patients following prolonged admission and is more slowly progressive. Prolonged use of neuromuscular blocking agents (e.g. vecuronium bromide) also may lead to persistent weakness and failure to wean from the ventilator
7. Functional illness	Vague sensory symptoms and odd pattern of weakness

36.6 Differential Diagnosis

The main differential diagnoses for PCB weakness are brainstem strokes, myasthenia gravis and botulism. In the early stages, paraparetic GBS can be difficult to distinguish from other conditions, such as lumbosacral plexopathy or cauda equina syndrome. MRI with gadolinium contrast of the lumbosacral region is, therefore, worthwhile to exclude an infiltrative or compressive cause of the paraparesis. Careful history taking and clinical examination should enable clinicians to differentiate bifacial weakness with paraesthesias from bilateral Bell's palsy in the majority of individuals. Typically, patients with bilateral Bell's palsy do not have distal paraesthesias and are likely to present with other features, including mastoid pain and hyperacusis; these patients are less likely to recover fully than are patients with bifacial weakness with paraesthesias. Rapidly progressive isolated bilateral facial weakness may also be present in patients with sarcoidosis or Lyme disease.

36.7 Management

36.7.1 General Measures

GBS is a potentially life-threatening disease. Both general medical care and immunological treatment are essential. Meticulous attention to supportive care is needed to prevent or to manage complications. Issues that need attention are monitoring respiratory function [Erasmus GBS Respiratory Insufficiency Score (EGRIS)] (Walgaard et al. 2010), cardiac and haemodynamic monitoring (autonomic dysfunction), prophylaxis for deep vein thrombosis, management of possible bladder and bowel dysfunction, early initiation of physiotherapy and rehabilitation and psychosocial support.

36.7.2 Immunological Therapy

Several randomised controlled trials studying the effect of immunotherapy in GBS are available. IVIg and plasma exchange have proved effective (Raphael et al. 2012; Hughes et al. 2014). If IVIg or plasma exchange will be started, they should, in principle, be started as soon as possible, before irreversible nerve damage has taken place. The volume of plasma removed or the optimum number of PE has not been established, but many physicians use the protocol of North American trial in which a total of 200–250 mL/kg was exchanged over 7–10 days.(The Guillain-Barré Syndrome Study Group 1985). In developing countries where cost is the limiting factor, small volume PE may be used. In India small volume PE was used by Tharakan et al. with comparable results. They used 15 mL/kg body weight/day to be continued till the progression of the disease got arrested or recovery started (Tharakan et al. 1990). It is started within the first 4 (preferably 2) weeks from onset in patients with GBS who are unable to walk unaided (GBS disability score > 2) (Raphael et al. 2012). Similarly, IVIg is proven to be effective, in patients unable to walk unaided, when started within the first 2 weeks after onset of weakness. Whether the total IVIg dose (2 g/kg bodyweight) given in 2 days (1 g/kg per day) is more beneficial than when given in 5 days (0.4 g/kg per day) is not known. It is better to give the total IVIg dosage in 5 days, because this regimen might induce fewer side effects and because children who receive a faster IVIg regimen are reported to have treatment-related fluctuations (TRFs) more frequently (Korinthenberg et al. 2005). About 10% of patients treated with IVIg or plasma exchange will deteriorate after initial improvement or stabilisation – i.e. they will have a TRF (Hughes et al. 2014). These TRFs usually occur within the first 8 weeks after start of treatment. Repeated treatment (2 g IVIg/kg in 2–5 days) has been observed to be beneficial in these patients. Although no RCTs have shown that retreatment is beneficial in case of a TRF, it is common practice in many centres to do so (Van Doorn 2013). Patients with GBS with a TRF are likely to have a prolonged immune response that causes sustained nerve damage or functional blockade, which needs more prolonged treatment than standard care. The inference of which is that they would be worse without therapy, rather than an indication of complete treatment resistance (Hughes et al. 2014).

Rather surprisingly, both oral steroids and intravenous methylprednisolone are not beneficial in the disorder (Hughes and van Doorn 2012). The combination of IVIg and methylprednisolone is not more effective than IVIg alone, although there might be some additional short-term effect after correction for known prognostic factors (Van Koningsveld et al. 2004). Combination of plasma exchange followed by IVIg is not significantly better than plasma exchange or IVIg alone (Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group 1997). No evidence exists that shows a second course of IVIg is effective in patients with GBS who continue to deteriorate. Researchers in the Netherlands are investigating whether patients with GBS with a poor prognosis, defined using the modified Erasmus GBS outcome scale (mEGOS), might benefit from a second IVIg course when given shortly after the first IVIg course (SID-GBS RCT trial) (Ruts et al. 2010). Because IVIg is more convenient to give, widely available and generally has only minor side effects, it has replaced plasma exchange as the preferred treatment in many centres. A disadvantage of IVIg is the high cost. In low-income countries, both IVIg and standard plasma exchange treatment might be too expensive for a large proportion of patients. A completely new approach is being investigated in an RCT of the drug eculizumab – a humanised monoclonal antibody that binds with high affinity to the complement factor C5 and prevents its cleavage to C5a and the pro-inflammatory, cytolytic C5b-9 complex (Halstead et al. 2008).

36.7.3 Tracheostomy and Ventilation

Tachypnoea, tachycardia, brow sweating, asynchronous movements of the chest and abdomen and a vital capacity <20 mL/kg, maximal inspiratory pressures <30 mm H_2O and maximal expiratory pressure < 40 cm H_2O prompt intubation and ventilator assistance. Ventilated GBS patients who are unable to lift the arms from the bed and patients who have axonal degeneration or inexcitable nerves at 1 week should undergo a tracheostomy (Walgaard et al. 2017). In mechanically ventilated patients with respiratory failure secondary to GBS, negative inspiratory force [NIF] less than −50 cm H(2)O and VC improvement pre-extubation to pre-intubation by 4 mL/kg are significantly associated with successful extubation. Failed extubation or the need for tracheostomy correlates with autonomic dysfunction, pulmonary comorbidities and prolonged stay in the ICU (Nguyen et al. 2006).

36.7.4 Autonomic Dysfunction

Acute dysautonomia is a significant cause of death in patients with GBS. Cardiac and haemodynamic disturbance manifesting as hypertension, postural hypotension and tachycardia occur in a majority of GBS patients. This is due to excessive sympathetic overactivity and parasympathetic underactivity. Severe dysautonomia occurs usually in severe cases at the peak of the deficit (Burns et al. 2001). Table 36.4 outlines therapies for the autonomic dysfunctions.

Table 36.4 Therapy of autonomic dysfunction

Tachycardia	Does not require treatment
Bradycardia or sinus arrest	Approach varies widely. The presence of tachycardia, increased daily variation in systolic blood pressure, reduced normal respiratory-induced heart rate variation and first episode of severe bradyarrhythmia reduce the threshold for insertion of pacemaker. Endotracheal suction may provoke bradycardia or asystole, and this can be reduced by hyperoxygenation
Hypertension	If severe, mean pressure greater than 125 mmHg, short-acting antihypertensive are preferable – labetalol, esmolol, nitroprusside infusion
Hypotension	Intravenous fluid Avoid diuretics If pronounced and persistent, search for other causes, such as sepsis, myocardial infarction, pulmonary thromboembolism, use of narcotics, positive-pressure ventilation
GI motility disorder	Suspension of enteral feeds, nasogastric suctioning, erythromycin, neostigmine
Hyponatraemia	Find out cause – SIADH or natriuresis. Best way to differentiate is by measuring central venous pressure. SIADH need fluid restriction, while natriuresis requires intravenous volume expansion
Deep vein thrombosis	Anticoagulant treatment
Pain and sensory symptoms	Opioid analogues, gabapentin, pregabalin, TCA, carbamazepine
Nutrition	High-energy and high-protein diet
Surveillance for infection	Weekly or more frequent sputum and urine cultures and blood count

36.8 Prognosis

Patient characteristics consistently related to poor prognostic outcome in GBS are higher age (aged 40 years and over), preceding diarrhoea (or *C. jejuni* infection in the past 4 weeks) and high disability at nadir. The EGOS, which is based on these three clinical characteristics, can be used 2 weeks after admission to predict the ability of the patient to walk at 6 months (Van Koningsveld et al. 2007). The mEGOS incorporates the Medical Research Council (MRC) Scale for Muscle Strength score instead of disability and can predict outcome as soon as 1 week after admission, when therapeutic interventions are probably even more effective (Walgaard et al. 2011). The risk of respiratory failure is associated with rate of disease progression, severity of limb weakness, peroneal nerve conduction block and low vital capacity. This risk can be predicted for individual patients using EGRIS, based on the severity of weakness (expressed as MRC sum score), onset of weakness and facial palsy, bulbar weakness or both (Walgaard et al. 2010). These models are presently not validated for use in children and patients with axonal forms of GBS.

In 90% of patients, GBS is monophasic, although up to 10% of patients develop recurrent or relapsing GBS (Kuitwaard et al. 2009). Despite appropriate immunotherapy, the overall mortality in patients with GBS is 9% and 17% are left with severe disability (Hughes et al. 2010). Patients can die in the acute progressive stage, most probably because of ventilatory insufficiency or pulmonary complications or from autonomic dysfunction including arrhythmia. However, death can occur at a late stage when a patient is discharged from an ICU to a general neurology ward, which further shows the importance of prolonged accurate monitoring and general care (Van den Berg et al. 2013).

Generally, no contraindication to the vaccination of patients who previously have had GBS seems to exist, except for patients who had had the disorder in the past 3 months or had vaccination-related GBS (Willison et al. 2016).

Most improvements happen in the first year, but patients might show further recovery even after 3 or more years. Most children show good recovery of neurological deficits after GBS, but many have persisting long-term residual complaints and symptoms including paraesthesias, unsteadiness of gait in the dark, painful hands or feet and severe fatigue (Roodbol et al. 2014). Recurrent GBS is seen in less than 10% of patients, but subsequent episodes seem to become more severe and occur at shorter time intervals (Mossberg et al. 2012).

36.9 Case Study

Clinical details: A 33-year-old male patient presented with history of tingling sensation and numbness in both palms and soles since 15 days. He also developed fatigue, pain in limbs and difficulty in climbing stairs since 4 days. He had loose motions prior to onset of these complains. There was no history of weakness of upper limbs, cranial nerve involvement, dyspnoea, autonomic dysfunction or bowel/bladder involvement. On examination, multiple, enlarged lymph nodes were palpable in inguinal region on right side. Pinprick and touch sensations were impaired in the foot and hands. Proprioceptive sensations were impaired till the ankles in lower limbs and fingers in upper limbs. There was mild proximal and distal weakness in lower limbs > upper limbs. All deep tendon reflexes were absent. Electrophysiological studies showed reduction in SNAP amplitude, delayed distal motor latencies, absent F waves and H reflex and temporal dispersion in CMAPs. These findings were suggestive of widespread, multifocal, sensorimotor demyelinating peripheral neuropathy suggestive of AIDP. CSF examination showed albuminocytological dissociation (proteins,140 mg, and cells – 2) favouring AIDP. CT abdomen was done to evaluate lymphadenopathy. It showed multiple centimetric-sized lymph nodes in the abdomen and inguinal region. Excision biopsy of inguinal lymph nodes was done which showed abundant lymphocyte infiltration and Reed–Sternberg cells (Fig. 36.2). It was later confirmed Hodgkin's lymphoma – nodular sclerosis. Later on, he developed severe proximal limb weakness and multiple cranial neuropathies. He was treated with IVIg and he showed good response.

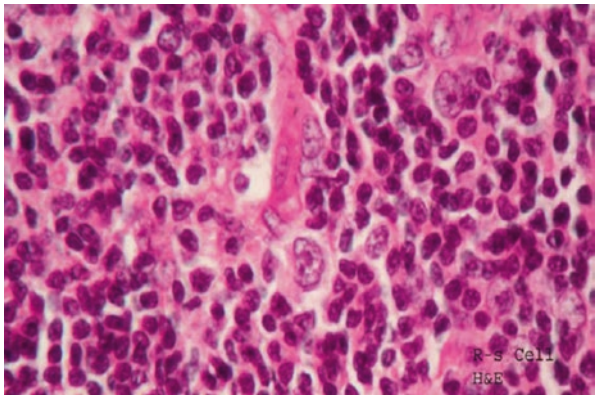

Fig. 36.2 Biopsy of inguinal lymph node showing loss of architecture, vascular proliferation, infiltrate of small and large lymphocytes with prominent nucleoli, Reed–Sternberg cells and presence of mitotic figures (Courtesy: Dr., Jamshed A. Lalkaka, Consultant Neurologist, Bombay Hospital, Mumbai)

Final diagnosis: paraneoplastic neuropathy secondary to lymphoma

Discussion: GBS-like illness can often be the heralding presentation of underlying systemic diseases such as haematological malignancies, vasculitic neuropathy, HIV neuropathy, porphyric neuropathy, neuropathies due to vitamin deficiencies and toxins and autoimmune disorders, e.g. Sjogren's syndrome. The following features in a patient with GBS-like presentation should alarm clinician to investigate for underlying disorder:

- Presence of systemic features like long-standing fever, weight loss, diarrhoea, abdominal pain, vomiting and lymph node enlargement
- Alteration in haematological parameters and elevated ESR
- Presence of severe pain in limbs
- Persistent asymmetry of symptoms
- Associated neuropsychiatric features
- Presence of CSF pleocytosis

Key Points

When to suspect

- Acute areflexic quadriparesis
- Acute sensory disturbances
- Acute autonomic failure

How to investigate

- Diagnosis of exclusion (Table 36.3)
- Hence, serum K+, porphyrins, toxins, etc.
- Electrophysiology showing demyelination or axonal changes (end of first week)
- Albuminocytological dissociation in CSF (second week)

How to treat

- IVIg or plasmapheresis
- Ventilatory assistance
- Treatment of autonomic dysfunction (Table 36.4)
- Supportive care
- Rehabilitation

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Charcot–Marie–Tooth Disease

37

37.1 Introduction

CMT is the most common group of inherited peripheral neuropathies. It is clinically composed of a heterogeneous set of disorders that range from mild to severe, some being asymptomatic and others resulting in stark limitations of daily activities. Patients present with weakness, atrophy and sensory loss (Fridman et al. 2015). Over 80 causative genes of CMT have been identified but many remain unexplored as yet (Rossor et al. 2013). Hereditary sensory neuropathy (or hereditary sensory and autonomic neuropathy) and distal hereditary motor neuropathy (or distal spinal muscular atrophy) are also included in the group of CMT (Hoyle et al. 2015).

37.2 Classification

CMT is classified according to mode of inheritance and degree of slowing of motor conduction velocity of median nerve. Autosomal dominant forms are most frequent. X-linked forms follow. Autosomal recessive inheritance is less common but should be considered in families having consanguinity and in sporadic cases. De novo mutations exist and reduced penetrance is encountered in some families.

These neuropathies are classified on the basis of nerve conduction parameters, into demyelinating and axonal groups. Demyelinating neuropathies are termed as CMT 1 and axonal, CMT 2. Lower limb nerves are often severely affected, and hence upper limb nerves prove more useful in the analysis. An upper limb motor nerve conduction velocity of more than 38 m/s is termed as axonal, and less than 38 m/s signifies demyelinating type (Harding and Thomas 1980). X-linked CMT patients show intermediate slowing between 35 and 45 m/s (Saporta et al. 2011).

Based on the pattern of inheritance and nerve conduction parameters, five main types can be distinguished (Table 37.1). Common genes and proteins involved in pathogenesis of CMT are depicted in Fig. 37.1 (Table 37.2).

S.V. Khadilkar et al., *Neuromuscular Disorders*,
https://doi.org/10.1007/978-981-10-5361-0_37

Table 37.1 Types of CMTs, their inheritance and conduction velocities

CMT Type	Mode of inheritance	Motor conduction velocities
1	AD or X	<38 m/s
2	AD or X	>38 m/s
4 or AR CMT 1	AR	Severe slowing
AR CMT 2	AR	>38 m/s
DICMT	AD	30–40 m/s

DI dominant intermediate
Berciano et al. (2012)

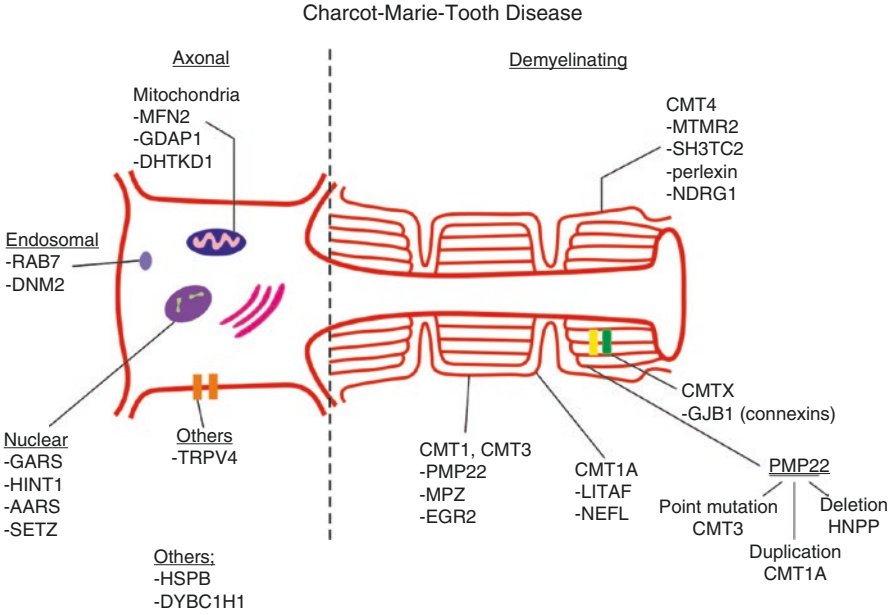

Fig. 37.1 Common genes and proteins involved in pathogenesis of axonal and demyelinating types of CMT

Table 37.2 CMT types, their genes and loci

CMT	Gene	Locus	Age of onset	Phenotypes
CMT 1				
1A	PMP22 duplication	17p11	All [common in 1st decade]	Classic form, hypertrophy of nerves
1B	MPZ	1q22	1st–2nd decade	More severe manifestations than CMT 1A
1C	LITAF	16p13	2nd decade	Gait changes, deafness and nerve hypertrophy in some patients

CMT	Gene	Locus	Age of onset	Phenotypes
1D	EGR2	10q21	1st decade	Scoliosis common A proportion have cranial neuropathies
1E	PMP22	17p12	Childhood	Deafness
1F	NEFL	8p21	1–13 years	Early and severe
CMT 'plus'	FBLN5	14q32	4th–5th decade	Macular degeneration Increased skin elasticity
CMT 2				
2A	MFN2	1p36	6 months to 50 years	Mainly distal, optic atrophy, central involvement
2B	RAB7	3q13	2nd decade	Sensory dominant, ulcers, Charcot joints, amputations
2C	TRPV4	12q24	Birth to 60 years	Mainly motor Hoarse voice Respiratory failure
2D	GARS	7p15	16–30 years	Distal upper limb; dHMN
2E	NEFL	8p21	1st–5th decade	Hearing loss. Hyperkeratosis
2F	HSPB1	7q11	Adult	Classic/dHMN
2G	Unknown	12q12	2nd decade	Classic
2I	MPZ	1q22	Late	Classic
2J	MPZ	1q22	Late	Pupillary abnormalities Hearing loss
2K	GDAP1	8q13	Variable	Voice changes Upper motor neuron signs
2L	HSPB8	12q24	15–33 years	Classic/dHMN
2M	DNM2	19p13	1st–2nd decade	Tremor
2N	AARS	16q22	15–50 years	Some have asymmetry of signs
2O	DYNC1H1	14q32	Early childhood	Learning issues in some patients
2P	LRSAM1	9q33	27–40 years	Mild and at times asymmetrical
2Q	DHTKD1	10p14	13–25 years	Classic
HMSN-P	TFG	3q13	17–55 years	Proximal involvement. Tremor. Diabetes mellitus
2W	HARS	5q31	Late onset	Sensory predominant
2U	MARS	12q13	Late onset	Motor–sensory
2	Mt-ATP6	Mitochondrial	1st–2nd decade	Mainly motor, some have upper motor neuron signs

(continued)

Table 37.2 (continued)

CMT	Gene	Locus	Age of onset	Phenotypes
CMT X				
1 [semidominant]	GJB1	Xq13	1st–2nd decade	Classic. Occasional patient develops hearing reduction
4 [recessive]	AIFM1	Xq26	Early childhood	Mental retardation. Deafness
5 [recessive]	PRPS1	Xq22	Childhood	Mild hearing loss, optic atrophy in advanced cases
6 [semidominant]	PDK3	Xp22	Childhood	Classic
Di CMT				
A		10q24.1–q25.1	7–72 years	Classic
B/2 M	DNM2	19p13	1st–2nd decade	Classic CMT with low white blood cell counts, early-onset cataract, ptosis, ophthalmoplegia
C	YARS	1p35	7–59 years	Classic
D	MPZ	1q22	30–50 years	Sensory loss and weakness. Deafness/ pupil disorders
E	INF2	14q32	5–28 years	Glomerulosclerosis and proteinuria
F	GNB4	3q26	5–45 years	Classic
CMT 4/AR CMT1				
A	GDAP1	8q13	<2 years	Severe and progressive. Voice changes and breathing difficulties
B1	MTMR2	11q22	3 years	Severe CMT1. Facial/ bulbar weakness. Scoliosis
B2	MTMR13[SBF2]	11p15	4–13 years	Severe CMT1. Glaucoma. Skeletal changes
B3	MTMR5 [SBF1]	22q13	5–11 years	Pes planus. Scoliosis
C	SH3TC2	5q23	Early-onset 1st–2nd decade	Severe to moderate CMT1 Hearing loss, skeletal changes
D	NDRG1	8q24	< 10 years	Severe CMT1. Deafness. Atrophic tongue, scoliosis
E	EGR2	10p21	Birth	Floppy child, multiple joint abnormalities, severe disability
F	PRX	19q13	Birth to first decade	Sensory features prominent

Table 37.2 (continued)

CMT	Gene	Locus	Age of onset	Phenotypes
G	HK1	10q22	8–16 years	Severe to moderate CMT1
H	FGD4	12q12	<2 years	Motor delay, skeletal changes and severe disability
J	FIG4	6q21	Congenital, childhood or adult	Severe disorder Features similar to ALS without bulbar signs Periods of rapid evolution known
K	SURF1	9q34	Childhood	Severe. Incoordination, brain MRI abnormalities and lactic acidosis
AR CMT 2				
A/B1	LMNA	1q22	2nd decade	Marked disability as distal to proximal progression
B/B2	MED25	19q23	28–42 years	Classic CMT2
C/B5	NEFL	8p21	1st decade	Severe form
F	HSPB1	7q11	Variable	Some patients have proximal weakness
H	GDAP1		1st decade	Voice changes, upper motor neurone signs
K	GDAP1		Early-onset form	Severe: Voice change, skeletal changes Milder: Autosomal dominant
P	LRSAM1	9q33	3rd–4th decade	Impotence, muscle cramps

37.3 Epidemiology

The spectrum of subtypes depends upon the population under study. In large cohort studies, in general, PMP 22 duplication, GJB1, MFN 2 and MPZ mutations and PMP 22 deletions account for most of the patients (Fridman et al. 2015).

37.4 Clinical Features

CMT neuropathies are very slowly progressive in nature, and hence it is often difficult for the patients to know clearly about the onset and early issues. Often, systematic history in the activities as infant, toddler and early childhood establishes that the symptoms have existed much longer than perceived. Mothers can tell the

differences in the motor performances of sibs accurately. Children often realise early on that they are not good as their peers in sporting activities but believe the 'that is the way they are' not realising the existence of disease. The same is the situation of skeletal abnormalities like pes cavus and kyphoscoliosis. Majority of patients have the symptoms since first or second decade of life, though form frusta and very mild forms can present in adulthood with minimum disabilities. Pain can be present in a proportion of patients and is believed to be related to the involvement of A delta fibres (Pazzaglia et al. 2010). Restless leg syndrome can be seen in a fourth of individuals (Harding and Thomas 1980); the recessive syndromes present earlier in life often at 2–3 years of age and evolve rapidly leading to early disabilities, as compared to the dominant ones (Tazir et al. 2013).

Examination findings are much more pronounced than the history would suggest, as the slow process allows time for functional adjustments. The main findings are of distal weakness, sensory loss and absence of deep tendon reflexes. Lower limbs are affected more than the upper limbs and foot drop is prominent. Nerves are thickened in the CMT 1 (Harding and Thomas 1980). The differential involvement of intrinsic foot extensors and the long extensor muscles over a period of years leads to the development of foot deformities like pes cavus and hammer toes. Similar abnormalities are also seen in the upper limbs in advanced cases. Scoliosis and kyphosis occurs in one third of patients. Hip dysplasia is rarely seen (Novais et al. 2014). The combination of skeletal abnormalities and neuropathy is very suggestive of an inherited neuropathy of the CMT type. Examination of family members is rewarding as findings are likely in individuals who are unaware of the existence of neuropathy.

Specific phenotypic features may exist in a particular type of CMT (Table 37.3). However, the phenotypic features are largely similar and overlap within subtypes; hence they have limited clinical value (Hoyle et al. 2015).

Table 37.3 Specific phenotypic features in CMT

Associated symptom	CMT type
Macular degeneration	1 [FBLN5]
Optic atrophy	2A2 [MFN2], K [GDAP1], X4 [AIFM1], X5 [PRPS1]
Glaucoma	4B2 [SBF2/MTMR13]
Cataract	DI B/2 M [DNM2]
Tonic pupils	2 J [MPZ], 1B [MPZ increased dosage]
Facial and bulbar weakness	4B1 [MTMR2], 4C [SH3TC2], HMN 7B [DCTN1]
Hearing loss	1E [PMP22],1F [NEFL],2E [NEFL],3 [PMP22, MPZ],4C [SH3TC2],2 J [MPZ], 4D [NDRG1],X1 [GJB1], X4 [AIFM1], X5 [PRPS1], DI E [INF2]
Tongue atrophy	4D [NDRG1]
Vocal cord paralysis	IA [PMP22], ID [EGR2], 2A2 [MFN2], 2C [TRPV4], 2 K [GDAP1], 4A [GDAP1], 7A [SLC5A7], AR CMT2H
Diaphragm paralysis	1A [PMP22] (SLEEP APNEA),2C [TRPV4], 2 J [MPZ] (COUGH), 3 [EGR2, PMP22],4A [GDAP1], 4B1 [MTM2]

Table 37.3 (continued)

Associated symptom	CMT type
Pyramidal signs	2 K [GDAP1], HMN 5A [BSCL2], HMN 5B [REEP1], AR CMT2H
Predominant hand wasting	2D [GARS], 2 L [HSPB8], HMN 5A [GARS], HMN 5B [REEP1], 5C [BSCL2]
Mutilating sensory neuropathy	2B [RAB7A]
Neuromyotonia	AR CMT2 [HINT1]
Scoliosis	2A2 [MFN2], 2C [TRPV4], 2D [GARS], 2 K [GDAP1], 2 L [HSPB8],AR CMT 2A [LMNA], 3 [PMP22, MPZ,PRX,EGR2], 4B1 [MTMR2], B2 [SBF2],4B3 [SBF1],4C [SH3TC2], 4H [FGD4], 4 J [FIG4]
Renal failure	DI E [IFN2]
Early proximal weakness	4B [MTMR2], 4B1 [MTM2], HMSN-P [TFG]
Erectile dysfunction	AR 2P [LRSAM1]

37.5 Investigations

37.5.1 Electrodiagnostic Studies (EDx)

The primary role of electrodiagnosis is twofold: firstly, to differentiate demyelinating from axonal processes and, secondly, to separate acquired from inherited neuropathies. The dysmyelinating neuropathies, on electrophysiology, do not show temporal dispersion and conduction blocks (Kaku et al. 1993). Instead, a symmetric, uniform involvement is seen. Comparing both sides for various parameters is hence important. Occasionally, findings mimic acquired demyelinating neuropathy in GJB1, MPZ, SH3TC2, SPTLC1, CMT4J and FIG4 mutations (Cottenie et al. 2013). Recessive disorders have more severe EDx parameters than the dominant ones (Tazir et al. 2013). In some congenital motor neuropathies, the compound muscle action potentials may be normal due to collateral sprouting (Rossor et al. 2015).

37.5.2 Cerebrospinal Fluid (CSF)

CSF analysis has limited role and protein elevation may be seen in demyelinating types, sometimes exceeding 100 mg per dl (Bouche et al. 1983).

37.5.3 Neuromuscular Ultrasound

Ultrasound examination forms an inexpensive modality to study the nerves. Demyelinating types of CMT exhibit uniform and diffuse nerve enlargements. This is in contrast to patchy and focal thickening seen in acquired demyelinating

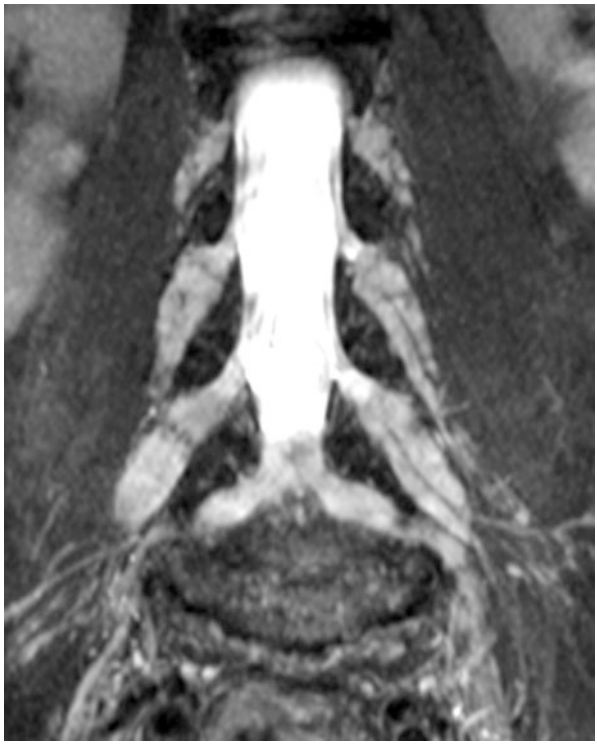

Fig. 37.2 MR neurography showing thickening of lumbosacral plexus in a patient with demyelinating type of CMT (Courtesy: department of radiology, Bombay hospital, Mumbai)

neuropathies (Zaidman et al. 2013; Schreiber et al. 2013; Sugimoto et al. 2013). In HNPP, the enlargement tends to be at entrapment sites, whereas it is diffuse in CMT 1A (Goedee et al. 2015).

37.5.4 Neuromuscular MRI

MRI studies are being increasingly utilised in the evaluation of neuropathies. It has the advantage of studying the proximal segments which are relatively inaccessible. MRI shows thickening of all nerves (Fig. 37.2), and denervation changes are seen in distal musculature (Berciano et al. 2010).

37.5.5 Nerve Biopsy

Biopsy currently is reserved for complex patients in whom there is a clinical suspicion of an acquired and potentially treatable inflammatory neuropathy (Rossor et al. 2015). In CMT patients, the sural nerve biopsy typically shows the changes of a hypertrophic neuropathy, characterised by onion bulb formation (Fig. 37.3). Onion bulb formation is not specific and is seen in multitude of conditions. Specialised studies can bring out changes in myelin and axons.

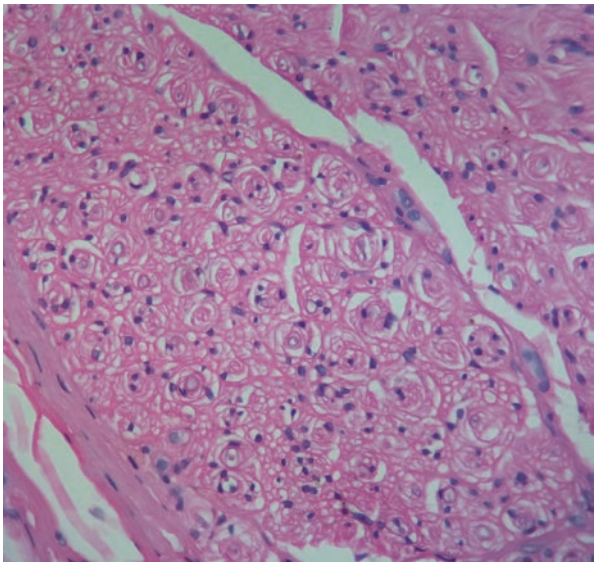

Fig. 37.3 HE (40×): Nerve fascicle with onion bulbs in CMT (Courtesy Dr. Dilip Jethwani)

37.5.6 Genetic Testing

Genetic testing was initially utilised in the diagnosis of PMP 22 deletion and duplications (Roa et al. 1991). Rapidly, more than 900 different mutations in more than 60 causative genes are now described. In spite of these advances, a large number of patients do not show known genetic abnormalities. Moreover, specific therapies have not yet evolved, so the scope of these genetic tests remains diagnostic and for counselling (Echaniz-Laguna 2015). The following strategies have been gainfully employed in the genetic testing of CMTs (Tables 37.4 and 37.5).

Table 37.4 Methods of genetic testing with their main features

Method	Features
Demyelinating neuropathy: Test for PMP22 duplication	Detects this common mutation Cost-effective
NGS panels can be applied to • A set of genes (panels) • All protein-coding genetic material (the exome) • All genetic material (the genome) (Ankala et al. 2015).	All known gene changes can be detected Variants of uncertain significance encountered (Hoyle et al. 2015)
Whole-exome or genome sequencing	Use if panel negative (Daud et al. 2015; Lupski et al. 2010). Limitations: Small tandem repeats, other copy number variations, epigenetic changes or mutations in mitochondrial DNA are not detected (Hoyer et al. 2014)

37.6 Differential Diagnosis

DIfferential diagnosis of CMT have been mentioned in table 37.5.

Table 37.5 Differential Diagnosis

Condition	Key differentiating features
Acquired inflammatory neuropathies	Shorter duration, no family history, electrophysiological findings (see case study)
Toxic neuropathies, e.g. drugs, heavy metals	Dysaesthetic sensorimotor neuropathy with skin and epithelial changes
Deficiency states (e.g. B12, copper)	Myeloneuropathy, sensory ataxia, no skeletal changes (Hoyle et al. 2015)
HNPP	Acute weakness events with recovery
FIG4 mutation	Acute weakness and wasting of one limb, on the background of a chronic demyelinating neuropathy (Cottenie et al. 2013; Nicholson et al. 2011)
dHMN and distal myopathies	No or minimal sensory involvement in dHMN Forearm flexors affected early in distal myopathies (Udd 2007) cardiomyopathies (Horowitz and Schmalbruch 1994)
HSN	Sensory predominant, autonomic features, ulcerations
Leukodystrophy	MRI brain shows confluent white matter changes
Familial amyloidosis	Prominent autonomic neuropathies, carpel tunnel syndrome in males, axonal neuropathy, abnormalities in protein or immunofixation electrophoresis
Fabry's disease	Small fibre dysaesthetic neuropathy, angiokeratomas in bathing trunk area, strokes at young age
Refsum's disease	Retinitis pigmentosa, deafness, ataxia, and ichthyosis
Tangier's disease	Enlarged orange tonsils, low HDL, sensory loss on trunk and limbs simulating syringomyelia
Mitochondrial disorders	Multisystem involvements in various combinations, skeletal changes

37.7 Management

Management of CMTs is a teamwork. Neurologist helps in evaluation, diagnosis and prognostication; surveillance of comorbidities; longitudinal care and re-evaluation; guide for lifestyle modifications; and referrals to genetic counsellors, OT/PT and mental health specialist and updates patients regarding research studies. Genetic counsellor guides in genetic testing, presymptomatic testing and preconception counselling.

37.7.1 Physical Therapy and Rehabilitation

Early institution of supportive therapy can have positive impact on the quality of life. As sensory and motor fibres are affected, stretching and strengthening exercises, balance and postural exercises and gait training become important. Patients

are likely to fall and injure themselves, and fall prevention strategies need to be discussed. Night splints can help reduce contractures, ankle–foot orthoses can improve gait (Ramdharry et al. 2012), thumb splints can improve hand functions (Videler et al. 2012) and a multitude of assist devices have now become available, which can be tailored to the individual case (McCorquodale et al. 2016).

37.7.2 Exercise

There have been positive views about benefits of resistance training (Piscosquito et al. 2014; Chetlin et al. 2004; Burns et al. 2009), and this has been suggested to patients with CMT. One concern is whether overwork will have negative impact on the condition, and this needs to be kept in mind and dealt with in individual cases, carefully monitoring the progress.

37.7.3 Role of Surgery

Surgical corrections are reserved for selected patients who have repeated ankle sprains or when pain persists in spite of orthoses. Needless to say, these need to be highly individualised to the given situation and involve realigning of the joints, bone formatting and correct muscle imbalance. Rarely, severe scoliosis may need corrective measures (Table 37.6).

37.7.4 Putative Therapies

Medications that can potentially cause neuropathy should be carefully evaluated and avoided whenever possible in CMT patients (Weimer and Podwall 2006).

Table 37.6 Putative Therapies

Therapeutic intervention	Proposed benefits
High doses of ascorbic acid	Downregulates PMP22 production in animal models, human trials not promising (Lewis et al. 2013; Micallef et al. 2009; Pareyson et al. 2011; Gess et al. 2013; Passage et al. 2004).
Progesterone antagonists	Decrease PMP22 production (Meyer zu Horste et al. 2007; Sereda et al. 2003)
Curcumin in CMT1B	Improved Schwann cell differentiation (Patzko et al. 2012; Bai et al. 2013)
Histone deacetylase 6 inhibition	Correction of axonal transport defects CMT2F (d'Ydewalle et al. 2011)
Combination of baclofen, naltrexone and sorbitol	Initially stabilisation followed by continued mild improvements (Attarian et al. 2014) pleiotropic mechanisms for downregulating PMP22 (Chumakov et al. 2014)
Neurotrophin 3	Improved axonal regeneration (Sahenk et al. 2005; Sahenk et al. 2014)
HDAC inhibitors	Improved axonal transport (d'Ydewalle et al. 2012)

37.8 Prognosis

In the CMT group as a whole, the extent of axonal loss correlated better with the degree of disability when compared with the extent of demyelination (Bouche et al. 1983).

CMT Neuropathy Score (CMTNS) has been designed to classify the condition in three grades, mild, moderate and severe. The score takes into consideration clinical and electrophysiological features of the case. As is expected, patients in severe category require assistance for ambulation, and those with moderated grade can ambulate with the use of orthosis. CMT Examination Score (CMTES) is similar to CMTNS, does not include electrophysiology and hence is simpler to apply (Shy et al. 2005).

37.9 Case Study 1

Clinical data: A 16-year-old boy was evaluated for weakness of lower limbs. Parents noticed that he was not able to walk and run as well as his elder sister, when he was 4 years of age. While he continued normal schooling activities, he lagged behind in the physical training classes and preferred to stay indoors and play video games. He had no sensory symptoms and his scholastic performance was satisfactory. He was born to consanguineous parents and two of his paternal cousins showed similar symptoms.

Examination showed pes cavus, thin build, mild kyphoscoliosis and thickening of all peripheral nerves. He had wasting and weakness of distal and semi distal muscles of all four limbs and mild proximal hip area weakness (Fig. 37.4). Sensations were lost in a glove and stocking manner till mid shin and up to wrists.

Investigations: Electrophysiology showed uniform slowing of sensory and motor nerves without conduction blocks or dispersion. The velocities were slowed by up to 50%. There was mild attenuation of the CMAPs and SNAPs. F waves were prolonged. MRI neurography showed severe thickening of the nerve roots of upper and lower limbs (Fig. 37.3).

Nerve	Latency		Duration		Amplitude		Conduction velocity
	Distal	Proximal	Distal	Proximal	Distal	Proximal	
Rt. median	4.2	11.8	17.4	17.7	7.2	6.3	30.22
Lt. median	4.06	13.5	16.0	17.2	6.4	5.6	26.37
Rt. ulnar	3.4	11.1	18.2	21.3	6.2	5.7	35.02
Lt. ulnar	3.9	13.4	16.7	15.8	6.2	4.7	26.37

F waves

	Minimum latency	Maximum latency	Persistence
Lt. median	50	61.2	All
Lt. ulnar	50	52.08	All
Rt. ulnar	44.79	52.5	All
Rt. median	48.5	50.83	All

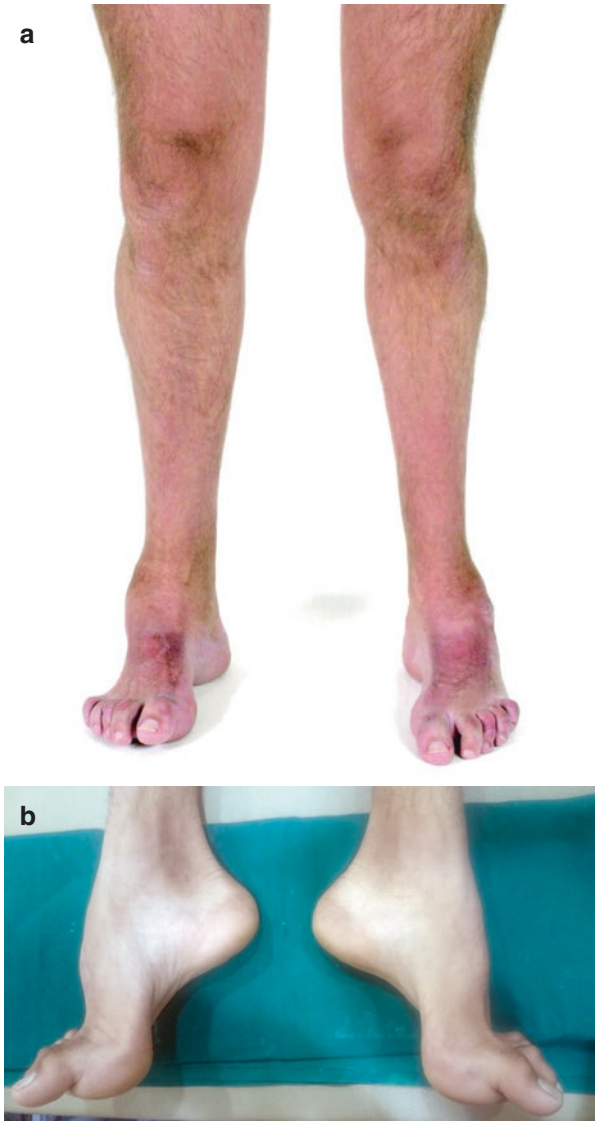

Fig. 37.4 (**a**) Inverted champagne bottle appearance and (**b**) pes cavus in CMT

Impression: slowly progressive demyelinating neuropathy

Q. 1: Is this an inherited or acquired form of demyelinating neuropathy? How to differentiate them?

Inherited demyelinating neuropathy	Acquired demyelinating neuropathy
Insidious onset and chronic course	Acute to subacute onset
Distal > proximal segments involved	Proximal > distal segments involved in majority
Wasting and weakness	Weakness>>wasting

Sensory signs >>symptoms	Sensory symptoms as well as signs
Other family members affected clinically or subclinically	Family history is not contributory
Musculoskeletal deformities, e.g. pes cavus, kyphoscoliosis ++	Usually no musculoskeletal deformities
CMT1, 2 and 4 show uniform conduction slowing	Multifocal conduction slowing
No conduction blocks except CMT X and HNPP	Conduction blocks and temporal dispersion are often present

Q. 2: What are the differences between axonal and demyelinating types of inherited neuropathies?

Axonal versus demyelinating inherited neuropathy

Demyelinating	Axonal
1st decade onset	2nd decade onset
Foot and spinal deformities more prominent	Less prominent deformities
Areflexia	Depressed reflexes
Tremors are more prominent	Less prominent
Thickening of nerves ++	Nerves not thickened
CMT 1, 3 and 4	CMT 2

Above factors favour inherited demyelinating neuropathy in this patient. On palpation, nerve thickening is often present. MR neurography can also help to demonstrate uniform nerve thickening at proximal sites. As we are dealing with an inherited demyelinating neuropathy, nerve biopsy would not contribute in reaching final diagnosis. Hence, genetic analysis was done which showed 1.5 mb duplication at 17p 11.2 region in the PMP 22 gene.

Final diagnosis: CMT 1

37.10 Case Study 2

Clinical data: A 20-year-old student noticed that her gait had changed gradually over preceding 5 years. She had to lift her left leg higher while walking and was unable to clear the ground on uneven surfaces. Foot wear tended to slipped off because of toe weakness and she often twisted her ankles. Her spine had also gradually bent to left side and forwards. Two years before presentation, she was finding it difficult to do fine precision work with her hands. She did not have any sensory symptoms. She had noticed the 'peculiar' shape of her feet. She was born of consanguineous marriage; her parents were first cousins.

She had severe kyphoscoliosis, pes cavus and hammer toes (Figs. 37.5 and 37.6). The ulnar and lateral popliteal nerves were thickened on palpation. She had weakness of dorsiflexion and plantar flexion of ankles and her intrinsic hand muscles were weak. Foot drop was evident on walking. The proximal power was unaffected. Sensory examination revealed striking findings. She had reduced pinprick sensation

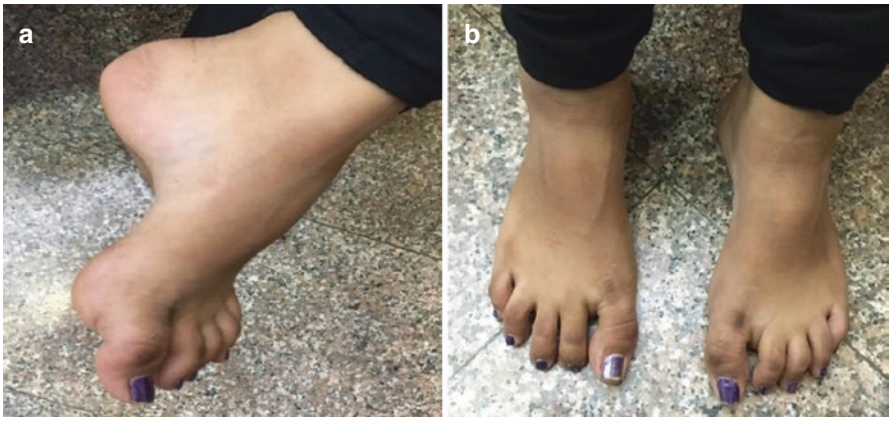

Fig. 37.5 (**a**) Pes cavus and (**b**) hammer toes

up to knees, vibration was decreased up to ankles and joint position was absent till ankles. Upper limb sensations were normal. She had total areflexia.

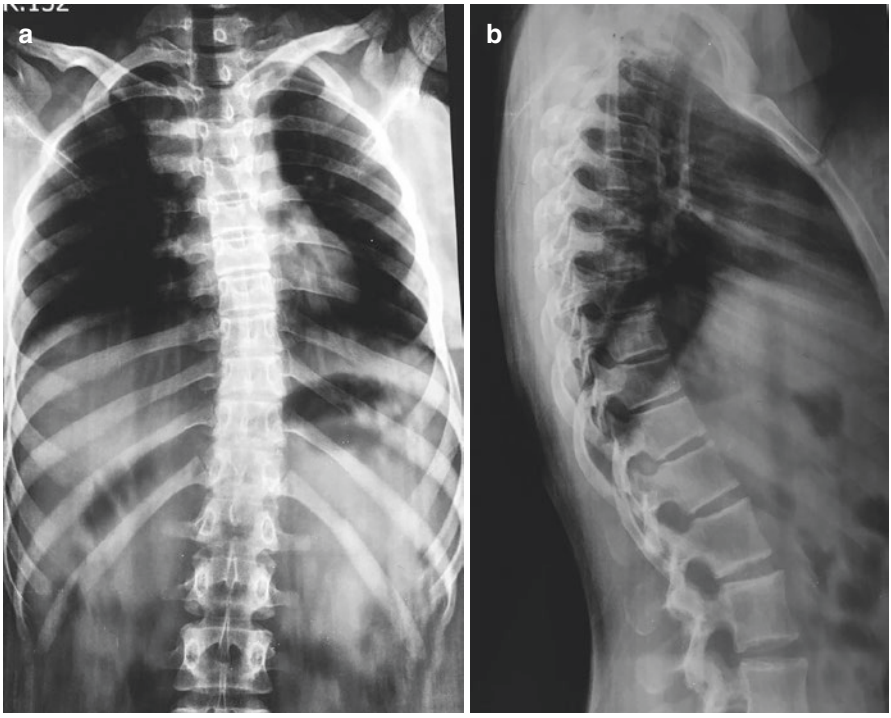

Fig. 37.6 (**a**) Scoliosis and (**b**) kyphosis on plain X-ray of dorsolumbar spine

Investigations: Her serum biochemistry was normal. Electrophysiology showed severe attenuation of SNAPS and sural nerves were not elicitable. Compound muscle action potentials were attenuated. There was uniform slowing of motor and sensory nerves in the demyelinating range, without any conduction blocks or dispersion. F waves were uniformly delayed.

MRI neurography showed thickening of the nerve roots.

Discussion: This patient has generalised, symmetrical, uniform, lower limb > upper limb predominantly demyelinating neuropathy. One striking feature is presence of prominent kyphoscoliosis. Kyphoscoliosis is known to occur in CMT4C as well as CMT1A, 1B and 1C. Genetic studies confirmed a homozygous pathogenic mutation in the SH3TC2(−) gene, exon 11, variant c.2775G > A (p.Trp925Ter).

Features of CMT 4C: Autosomal recessive, early-onset demyelinating neuropathy, severe progression, inability to walk till adolescence, nerve conduction velocities 20–30 m/s and radiology may show hypertrophic nerve roots.

Final diagnosis: CMT 4C

Key Points

When to suspect

- Chronic progressive weakness and sensory loss
- Length-dependent evolution
- Thickened nerves in dysmyelinating types
- Skeletal deformities (pes cavus, hammer toes, kyphoscoliosis)

How to diagnose

- Mode of inheritance
- Age at presentation and helpful clinical features (Table 37.3)
- Electrophysiology: case 1 Q1 and Q2
- Genetic studies

How to treat

- Avoid triggers in HNPP
- Ankle foot orthoses and surgical corrections

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Chronic Inflammatory Demyelinating Polyradiculoneuropathy

38

38.1 Introduction

Since the 1950s, recognition of polyneuropathies with progressive and relapsing course has increased. Dyck and his colleagues were one of the first to describe these as 'chronic inflammatory polyradiculoneuropathies'. It was also observed that these patients responded to steroids, suggesting immune causations of this disorder. Later, electrophysiological and histopathological examination revealed demyelination as the underlying pathology. Due to demyelinating nature of this illness, the term 'chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)' came into existence. Initially, CIDP was considered to a homogeneous disorder. Later on, a number of immune-mediated demyelinating neuropathies were found to have varying similarities to CIDP. Some of the systemic disorders can present as CIDP and are known as secondary CIDP. Variants of CIDP and causes of secondary CIDP are enlisted in Table 38.1.

38.2 Epidemiology

The prevalence of CIDP ranged from 1.97 to 4.77/100,000 depending on the diagnostic criteria used (Rajabally and Chavada 2009).

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Table 38.1 CIDP variants

Typical CIDP	
CIDP variant	1. Pure motor variant 2. Pure sensory variant 3. Focal CIDP 4. Multifocal acquired demyelinating sensory and motor neuropathy [MADSAM] 5. Distal acquired symmetrical demyelinating neuropathy [DADS] 6. Chronic immune sensory polyradiculopathy [CISP] 7. Chronic immune motor polyradiculopathy [CIMP] 8. Chronic immune sensory motor polyradiculopathy [CISMP]
Secondary CIDP	1. HIV-1 infection 2. Systemic lupus erythematosus 3. Monoclonal gammopathy of undetermined significance (MGUS) 4. Plasma cell dyscrasias (macroglobulinemia, osteosclerotic myeloma, POEMS syndrome, Castleman disease) 5. Chronic active hepatitis 6. Inflammatory bowel disease 7. Hodgkin lymphoma 8. Drugs: Tacrolimus, TNF-α antagonists including etanercept, infliximab and adalimumab

38.3 Clinical Features

CIDP usually peaks during fifth and sixth decades of life but can be seen across all ages. Younger age of onset tends to have more acute-onset, relapsing course and more prominent gait abnormalities. Based on temporal evolution, three patterns of CIDP exist:

- Continuous or stepwise progressive course over months is the most common form and is seen in more than 60% of the patients.
- One third of the patients develop a relapsing course. Such patients develop partial or complete recovery between recurrences.
- Rarely, CIDP has a very acute presentation and is known as acute-onset CIDP.

Most patients have symmetrical motor and sensory involvement at the onset. Due to non-length-dependent involvement in CIDP, proximal weakness is as severe as or more pronounced than distal limb weakness. Both lower and upper limbs are affected, but lower limb involvement is more severe and early than upper limb involvement in most cases. Weakness can involve facial, bulbar, neck and, occasionally, respiratory muscles. Muscle wasting is rare even in presence of severe motor deficits.

Deep tendon reflexes are diffusely diminished or absent even in presence of mild weakness. Sensory impairment usually occurs in a glove-stocking pattern. Large fibre involvement is far more pronounced than small fibres. Hence, paraesthesias

and imbalance while walking commonly occur, while pain and dysesthesias occur less frequently.

Additional features that can occur are postural tremors of the hands, enlargement of peripheral nerves, disc oedema and autonomic dysfunction. Extreme nerve root enlargement can rarely lead to lumbar canal stenosis, myelopathy and pseudotumour cerebri. CIDP may be associated with multifocal CNS demyelination but is extremely uncommon (Midroni and Dyck 1996). It is important for clinicians to be aware of the fluctuations either due to true relapse or worsening of symptoms due to dose reduction. MADSAM is a variant of CIDP that closely resembles typical CIDP, and both conditions need to be differentiated. Presence of older age of onset, prominent upper limb involvement, relatively rapid progression and more severity and less common involvement of cranial nerves favour typical CIDP (Kuwabara et al. 2015). Atypical presentations of CIDP have been described below:

38.3.1 Sensory CIDP

Intriguingly, a small proportion (5–15%) of patients with demyelinating neuropathies present as pure sensory syndrome. Such patients do not have weakness and are termed as 'CIDP'. It is still unclear whether patients with pure sensory syndrome and asymptomatic motor involvement on electrophysiology should be included under the umbrella of sensory CIDP or not (Busby and Donaghy 2003; Rotta et al. 2003).

38.3.2 Motor CIDP

Few patients with CIDP tend to have isolated motor involvement. It is important to identify this subgroup as they do not respond or worsen with corticosteroids. However, they improve with IVIg. It is yet to be confirmed whether pure motor CIDP is distinct from MMN considering that both have pure motor involvement, poorly respond to corticosteroids and show improvement with IVIg. It is still unclear whether presence of subclinical sensory involvement on electrophysiology is permissible in pure motor CIDP (Donaghy et al. 1994; Sabatelli et al. 2001; Kimura et al. 2010).

38.3.3 Focal CIDP

Thomas et al. (1996) reported nine patients, including five who had a sensorimotor impairment in one or both upper limbs, one with sensory impairment restricted to one limb and three restricted to purely motor impairment involving one or two upper limbs. Another patient with a chronic sensory neuropathy restricted to one

limb over a period of 30 years without any weakness (Ayrignac et al. 2013). However, all these patients with focal neuropathy improved with corticosteroids or IVIg, which led to their inclusion under the term 'focal CIDP'. It is rather intriguing for CIDP (which is caused by systemic immune response against nerve myelin) to cause focal impairment.

38.3.4 MADSAM

Please refer to chapter on MADSAM.

38.3.5 DADS

Please refer to chapter on DADS.

38.3.6 CISP, CIMP and CISMP

These are focal forms of CIDP wherein only the proximal segment of sensory, motor or both roots are affected by the immune process and the distal segments are normal. These are difficult to diagnose, and MRI neurography and electrophysiology are important tests for the diagnosis. Salient clinical and investigational features of CISP, CIMP and CISMP are summarised in Table 38.2.

Table 38.2 Salient clinical and investigational features of CISP, CIMP, CISMP

Salient features	CISP (Sinnreich et al. 2004)	CIMP (O'Ferrall et al. 2013)	CISMP (Khadilkar et al. 2017)
Clinical features	Gait ataxia, large fibre sensory loss, paraesthesia and frequent fall	Chronic, progressive lower motor neuron weakness of the legs	Sensory ataxia and weakness
Differential diagnosis	MFS, Sjogren's syndrome, syphilis, SCA	LS radiculopathy, sarcoidosis, CMT, malignancy	
EDX	Normal SNAP, abnormal SSEP	Polyradiculopathy	Normal distal motor and sensory examination, absent F waves, abnormal SSEP
MRI LS spine/ neurography	Lumbosacral roots thickening and contrast enhancement		
CSF	Albuminocytological dissociation		
Response to immunomodulators	Favourable		

38.3.7 CIDP in Association with Diabetes and Myeloma

It is observed that CIDP tends to occur more frequently (up to ten times) in patients with both insulin-dependent and non-insulin-dependent diabetes mellitus. These patients with diabetes mellitus and CIDP respond favourably to IVIG therapy (Sharma et al. 2002). As there is molecular mimicry between melanoma and Schwann cells, occasionally patients with malignant melanoma or after therapy by vaccination with melanoma lysates can develop CIDP (Weiss et al. 1998). Hence, it is important to rule out these illnesses that can present with CIDP before considering the diagnosis of idiopathic CIDP.

38.4 Pathophysiology

A lot of data supports the role of humoral and cellular response to myelin sheath of peripheral nervous system in pathogenesis of CIDP, although, precise antigenic targets of this immune response are still unknown. Presence of different clinical patterns and difference in therapeutic response amongst various CIDP variants support different pathogenetic mechanisms in these diseases (Nobile-Orazio 2014).

38.5 Investigations

Electrodiagnostic study, CSF examination, MRI lumbosacral spine, blood count, ESR, serum and urine electrophoresis with immunofixation and skeletal bone survey are useful.

38.5.1 Diagnostic Criteria

As many clinical variants are described, it is necessary to define the clinical boundaries of this neuropathy. There are at least 15 different diagnostic criteria available in literature. Most of these include similar clinical features but differ in terms of the electrophysiological criteria necessary for its diagnosis (Bromberg 2011). Recently, Koski et al. (2009) considered presence of symmetric neuropathy affecting all four limbs, proximal weakness in at least one limb and excluding other causes (serum paraproteins or genetic abnormality) to be sufficient for CIDP. However, it dilutes the importance of electrophysiology. These criteria have shown to have higher sensitivity than that of the criteria of the American Academy of Neurology (AdHoc Subcommittee 1991) but lower than that of the EFNS/PNS (Joint Task Force of the EFNS and the PNS 2010) with a comparable specificity for the diagnosis of CIDP. The EFNS/PNS criteria appear to have the best combination of sensitivity (73%) and specificity (90%) for the diagnosis of CIDP (Joint Task Force of the EFNS and the PNS 2010).

38.5.2 Electrophysiological Study

It shows demyelinating neuropathy. Various electrophysiological criteria are used to diagnose CIDP as mentioned above. Typical CIDP usually have multifocal demyelination along distal, intermediate and proximal nerve segments affecting both sensory and motor system. Distal and intermediate segments are affected more frequently in CIDP as compared to its variants. As compared to typical CIDP, intermediate segments tend to be more affected in MADSAM. Intriguingly DADS remain localised to distal nerve segments, while CISP, CIMP and CISMP tend to be restricted only to proximal segments. Presence of F-wave abnormalities and prolonged latency at nerve roots on somatosensory evoked potential help to evaluate involvement of proximal segments and nerve roots in these variants of CIDP (Kuwabara et al. 2015, Allen and Lewis 2015, Devic et al. 2016).

38.5.3 Ultrasound

The Bochum ultrasound score (BUS) showed a sensitivity of 90% and specificity of 90.4% in distinguishing CIDP from AIDP, when they showed no differences in disease duration ($p = 0.0551$). In addition, the BUS distinguished subacute CIDP from AIDP with a sensitivity of 80%, specificity of 100% (Kerasnoudis et al. 2014).

38.5.4 CSF Study

Elevation of CSF proteins indicates inflammation of nerve roots. In most cases, CSF protein is more than 45 mg/dL in most (>95%) cases. It is common to detect CSF protein levels >100 mg/dL. CSF pleocytosis is rare and should raise suspicion of some infection or coexisting systemic illness, e.g. HIV-associated CIDP. Elevated cerebrospinal fluid protein levels also help to differentiate amongst different variants of CIDP as patients with typical CIDP tend to have significantly higher levels as compared to MADSAM and MMN (Kuwabara et al. 2015).

38.5.5 MRI Neurography

MRI neurography has been recently used to study the proximal nerve segments which are otherwise difficult to assess (Fig. 38.1).

38.6 Differential Diagnosis

Following diseases need to be differentiated from CIDP. Differential diagnosis of CIDP with their key distinguishing features is described in Table 38.3.

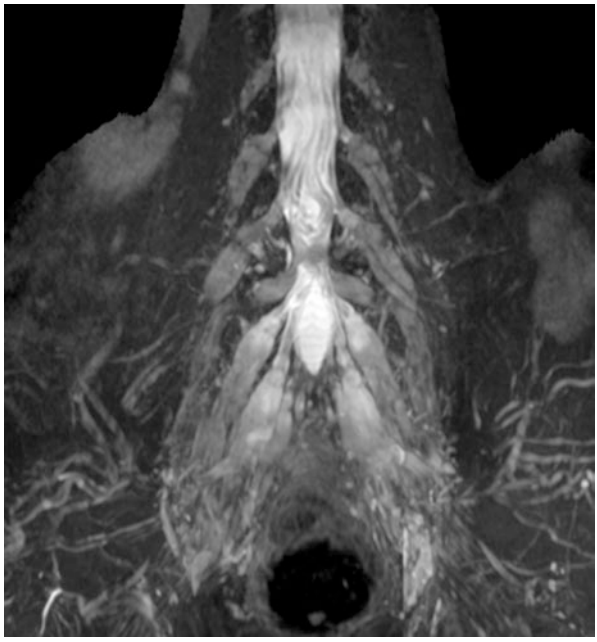

Fig. 38.1 MR neurography images showing extreme thickening of lumbosacral nerve roots in CIDP (Courtesy: Department of Radiology, Bombay Hospital, Mumbai)

Table 38.3 Differential diagnosis of CIDP with their key distinguishing features

Differential diagnosis	Key distinguishing features
GBS particularly should be differentiated from acute presentation of CIDP	Acute-onset, shorter course of illness, poor response to corticosteroids, and presence of antecedent infection favour GBS Acute CIDP is less likely to have autonomic dysfunction, cranial nerve involvement and respiratory impairment
Monoclonal gammopathy	Older age of onset, protracted course of illness, less severe disability and less favourable response to immunomodulation point towards monoclonal gammopathy

38.7 Management

Approximately 50–70% of the patients respond to either of the first-line immunomodulatory agents such as corticosteroids, plasma exchange and IVIg. Corticosteroids have been used as intravenous methylprednisolone (IVMP) pulses, as oral pulse methylprednisolone or as oral continuous prednisolone. The pulse methylprednisolone groups have fewer side effects while maintaining efficacy (Lopate et al. 2005; Muley et al. 2008). Recent Cochrane reviews have summarised efficacy of corticosteroids, plasma exchange and IVIg in CIDP (Mehndiratta and Hughes 2012; Mehndiratta et al. 2012 and Eftimov et al. 2013). Half of the patients, who initially don't respond to one of these agents, show favourable response on

switching to other therapy. Overall, about 80% of patients respond to one of these therapies (Cocito et al. 2010 and Viala et al. 2010). Decision to choose therapies depends upon efficacy, cost and side effects of each of these therapies.

Few randomised control trials comparing the efficacy of IVIg and intravenous methylprednisolone (IVMP) are available. One of them has shown that efficacy and tolerance of IVIg during the first 6 months of treatment was higher as compared to IVMP therapy. However, relapses were less frequent in IVMP group following discontinuation of therapy (Nobile-Orazio et al. 2012). On long-term follow-up, the median time to deterioration was significantly longer after discontinuing IVMP (14 months) than IVIg (4.5 months). However, proportion of patients who worsened after discontinuation of therapy was found to be similar in both subgroups (Nobile-Orazio et al. 2013).

As CIDP is chronic and medications have to be used for a long time, other immunosuppressants have been employed in the therapy of CIDP, though there is little evidence of their efficacy from randomised controlled trials (Mahdi-Rogers et al. 2013). Uncontrolled and retrospective trials have shown 30–82% benefits for various immunosuppressive agents, including the newer agents like interferon alpha, rituximab, etanercept and autologous haemopoetic stem cell transplantation (Mahdi-Rogers et al. 2013). When patients do not respond to the first line of therapy adequately, using these agents can increase the yield by 20–30%, but the side-effect profile also deteriorates (Cocito et al. 2011).

The following algorithm can be considered while planning therapy of CIDP (Fig. 38.2).

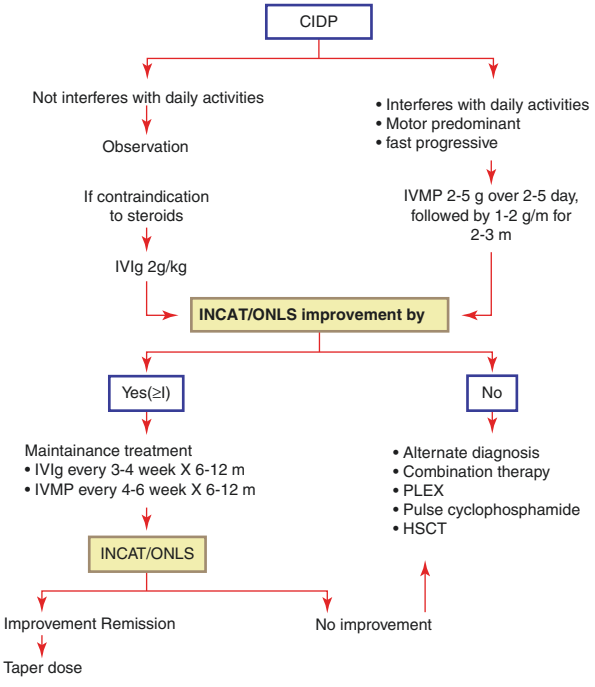

Fig. 38.2 Overview of management of CIDP

38.8 Prognosis

CIDP is a chronic condition and runs an indolent, fluctuating course. Spontaneous remissions are uncommon and half of the patients are severely disabled in spite of therapy (Chiò et al. 2007). Initiation of immunotherapy is uniformly rewarding, but the initial benefits are often not sustained and complete remissions are very uncommon. The presence and degree of axonal loss have been considered responsible for incomplete recovery.

38.9 Case Study

Clinical features: A 46-year-old male patient presented with complains of gradually progressive, tingling/numbness sensation in both lower limbs since last 2 years. There was also slippage of footwear without knowledge and imbalance while walking which used to worsen with eyes closed and in dark. He had mild difficulty in getting up from sitting position. There was no history of slippage of objects from hands, back pain, bowel/bladder involvement, weakness of upper limbs or cranial nerve involvement. On examination, proprioceptive loss was the most important and prominent finding. Vibration sensation was impaired up to the iliac spine and joint position sense was lost up to ankles. Romberg's test was positive. There was no weakness in lower limbs. All deep tendon reflexes were absent.

Summary: A 46-year-old male patient presented with gradually progressive sensory ataxia and areflexia without any weakness.

Discussion: Possible sites of localization of sensory ataxia are peripheral nerves, roots, dorsal root ganglia (DRG) and dorsal column. Points favouring and against these sites are summarised in Table 38.4:

Electrophysiology is extremely helpful to differentiate between nerve and preganglionic root lesion. NCS showed normal CMAPs and SNAPs. Absence of tibial–gastrocnemius H reflexes was the only abnormality detected on NCS. Electrophysiological findings favoured possibility of proximal site of lesion (preganglionic roots) as postganglionic segment was entirely preserved. SSEP was absent from nerves of lower limbs, further strengthening preganglionic root lesion.

Table 38.4 Differential diagnosis of sensory ataxia in this patient

Points favouring	Points against
Peripheral nerves—gradually progressive sensory ataxia and areflexia	Peripheral nerves—absence of small fibre and motor involvement is unusual for peripheral neuropathy
Roots—gradually progressive sensory ataxia and areflexia	Roots—symmetry of deficits and absence of pain
DRG—gradually progressive sensory ataxia and areflexia	DRG—symmetrical deficits, absence of upper limb involvement and pain
Dorsal column—gradually progressive sensory ataxia	Dorsal column—areflexia and absence of pyramidal signs

CSF examination and MRI contrast study of lumbosacral roots was done to evaluate pathology affecting preganglionic roots. CSF showed albuminocytological dissociation. MRI showed thickening and contrast enhancement of lumbosacral nerve roots. These findings favoured inflammation/demyelination affecting lumbosacral roots. ESR, calcium, angiotensin converting enzyme (ACE), HIV, CT thorax and abdomen were normal. Hence, possibility of atypical form of CIDP localised to preganglionic nerve roots was considered. Patient was treated with steroids and he showed remarkable improvement in symptoms, in spite of prolonged course of illness. CISP is a distinct and focal form of CIDP. It is unusually slow as compared to other forms of CIDP. It should be suspected when SNAPs are normal in cases of sensory ataxia and areflexia. It is potentially treatable even till late into the illness.

Key Points

When to suspect

- Subacute or chronic sensorimotor neuropathy
- Fluctuations in severity

How to investigate

- Elevated CSF protein
- Electrophysiology showing features of acquired demyelination
- Exclusion of secondary causes (IFE, search for myeloma, POEMS)

How to treat

- Chronic immunomodulation

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X-Linked Charcot–Marie–Tooth Disease 39

39.1 Introduction

In 1988, Herringham recognised a family of hereditary neuropathy in which males were selectively affected and was followed by Morgan's demonstration of X-linked inheritance in 1910. In the next 100 years, X-linked inherited neuropathy (CMT1X) was reported infrequently; its existence was briefly questioned (Harding and Thomas 1980) but has now emerged as the second most common form of CMT1 (Latour et al. 2006; Saporta et al. 2011). Many Cx32 mutants fail to form functional GJs or form GJs with abnormal biophysical properties. Schwann cells and oligodendrocytes express Cx32, and the GJs formed by Cx32 play an important role in the homeostasis of myelinated axons (Scherer and Kleopa 2012). Classification of CMT X has been tabulated below (Table 39.1).

Table 39.1 Classification of CMT X

Type	Gene	Locus	Inheritance	Phenotype
1	GJB1 (CX32)	Xq13.1	Dominant/ semidominant	Classic CMT, CNS involvement ±
2	?	Xp22.2	Recessive	Intermediate CMT, mental retardation
3 (Huttner et al. 2006)	?	Xq26.3–q27.1	Recessive	Pain and paraesthesia before the onset of sensory loss, spastic paraparesis
4	AIFM1	Xq24–q26.1	Recessive	Cowchock syndrome
5 (Kim et al. 2005)	PRPS1	Xq21.31–q24	Recessive	Deafness and optic atrophy
6 (Kennerson et al. 2013)	PDK3	Xp22.11	Semidominant	Deafness, tremor
Sensory neuropathy + deaf (Wang et al. 2006)		Xq23	Recessive	Deafness

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39.2 Epidemiology

The X-linked form of Charcot–Marie–Tooth disease (CMT1X) is the second most common form of hereditary motor and sensory neuropathy. Affected males have moderate to severe symptoms, whereas heterozygous females are usually less affected.

39.3 Clinical Features

Usual onset in males is around 10 years of age. The initial symptoms include difficulty in running and frequent ankle sprains. Weakness, atrophy and sensory loss start distally in lower limbs and progress to involve gastrocnemius and soleus, and hand muscles are affected later. As compare to CMT1A, muscle atrophy, particularly of intrinsic hand muscles, positive sensory phenomena and variable sensory loss are more prominent in CMT1X (Scherer and Kleopa 2012). Split hand phenomenon has also been observed. Female carriers usually have later onset than male and milder version of same phenotype (Scherer and Kleopa 2012).

CNS manifestations like acute transient encephalopathy, often triggered by high altitude, intense physical activities, acute infections, dehydration or hyperventilation have been described (Srinivasan et al. 2008). The duration of such central nervous system manifestation varies but usually resolves between a few hours and a few weeks. However, cerebral recovery, as seen by MRI, typically lags by months (Wang and Yin 2016). Some patients have mild, static clinical abnormalities. For example, fixed spasticity, hyperreflexia, dysarthria and ataxia have been reported. Findings indicative of corticospinal dysfunction in patients with fixed abnormalities and in patients with florid acute syndromes suggest that this tract may be a selectively vulnerable (Abrams and Freidin 2015). Central nervous system manifestations do not appear to correlate with the stage and severity of peripheral neuropathy; in some cases they are the initial manifestation of CMTX, while in others with exceptionally severe neuropathy, no clinical central nervous system phenotypes are present.

39.4 Pathophysiology

Connexins belong to a multigene family encoding 20 highly homologous proteins (Willecke et al. 2002). Six connexins form a hemichannel (or connexon), arranged around a central pore (Nakagawa et al. 2010). Two apposed hemichannels form a functional channel that provides a contiguous pathway between the adjacent cells or cell compartments. The channel diameter is too small to allow transfer of proteins and nucleic acids but large enough to allow the diffusion of ions and other small molecules (<1000 Da) (Scherer and Kleopa 2012). Many cell types, including oligodendrocytes and Schwann cells, express Cx32. Despite this broad expression pattern, peripheral neuropathy is usually the sole clinical manifestation of GJB1

mutations. The co-expression of other connexins may 'protect' some tissues against the loss of Cx32. Oligodendrocytes, for example, also express Cx47, and the loss of both Cx32 and Cx47 is far more deleterious than the loss of either one alone (Menichella et al. 2003; Odermatt et al. 2003). Cx32 is localised to non-compact myelin of incisures and paranodes (Bergoffen et al. 1993), where it likely forms these GJs between the layers of the Schwann cell myelin sheath (Balice-Gordon et al. 1998). A radial pathway formed by GJs at these locations would be up to 300-fold shorter than the circumferential pathway within the Schwann cell cytoplasm. It still remains to be shown that GJB1 mutations disrupt this shortcut, as well as the exact role this pathway plays in the homeostasis of myelinated axons.

Connexins is a complex molecule which is composed of 20 homologous proteins (Willecke et al. 2002). Six connexions surround the central pore and form a hemichannel (or connexion) (Nakagawa et al. 2010). Two hemichannels are placed in such a way that they provide a functional pathway between adjacent cells. This functional channel aka 'gap junctions' is meant to allow diffusion of smaller molecules like ions but blocks the transfer of larger molecules like proteins and nucleic acids (Scherer and Kleopa 2012). Some tissues such as oligodendrocytes and Schwann cells express Cx32. Schwann cells predominantly express Cx32, while oligodendrocytes express both Cx32 and Cx47. Hence, peripheral neuropathy is the most prominent manifestation of gap junction mutations as co-expression of connexins in oligodendrocytes seems to protect it from the loss of Cx32 (Menichella et al. 2003; Odermatt et al. 2003). These connexions are localised to non-compact myelin of paranodes in the peripheral nervous system where they form gap junctions between the layers of the Schwann cell myelin sheath (Bergoffen et al. 1993; Balice-Gordon et al. 1998). The radial arrangement of these connexions across the myelin sheath makes it 300-fold shorter than the circumferential pathway within the Schwann cell. However, the exact role of these functional pathways in the homeostasis of myelinated axons and its disruption by GJB1 mutations still remains largely unknown.

39.5 Investigations

39.5.1 Electrophysiological Study

Patients have 'intermediate' slowing of nerve conduction velocities, 30–40 m/s in affected males and 40–50 m/s in affected females, in forearm segments. Additionally, distal motor and F-wave latencies are mildly prolonged. Velocities are faster than CMT1 patients and slower than CMT2 patients, so termed as intermediate. Compared with CMT1A, conduction slowing in CMT1X is less uniform among different nerves and dispersion is more pronounced. In addition to conduction slowing, there is electrophysiological evidence of axonal loss in distal segments particularly the peroneal and tibial motor responses in lower limbs and the median and ulnar motor amplitudes in upper limbs. Needle electrode examination (NEE) confirms the length-dependent loss of motor units (Scherer and Kleopa 2012).

Corresponding to the clinical findings of disproportionate thenar involvement, median nerve conductions appear to be generally more severely affected than those of the ulnar nerve (Abrams and Freidin 2015).

39.5.2 Nerve Biopsy

Most prominent biopsy findings are of age-related loss of myelinated fibres and, in parallel, an increasing number of regenerated axon clusters. Many myelin sheaths are inappropriately thin for axon diameter suggestive of chronic segmental demyelination and remyelination or remyelination after axon degeneration (Scherer and Kleopa 2012).

39.5.3 MRI Brain

It shows various degrees of white matter hyperintense lesions (Wang and Yin 2016).

39.6 Differential Diagnosis

Please refer to HMSN differential diagnosis section.

In addition, based on the white matter lesions seen in MRIs, various possible diagnoses include drugs, toxins, inherited metabolic disease such as adrenoleukodystrophy or infectious and inflammatory causes such as acute disseminated encephalomyelitis and Guillain–Barré syndrome.

39.7 Management

Currently, there is no effective therapy available for CMTX. Putative therapies have been used in an attempt to decrease the progression of CMT, as a group (refer to management of CMT).

39.8 Prognosis

Genetic counselling can inform patients of the chance that they will pass CMTX on to their children. A female who is affected with an X-linked form of CMT has a 50% chance of passing down the condition in each pregnancy, no matter the sex of the child. As a hallmark of X-linked inheritance is that fathers do not pass the condition on to their sons, since the father needs to pass on his X chromosome to his daughters, all daughters born to a father with an X-linked form of CMT will be affected with the condition (Wang and Yin 2016).

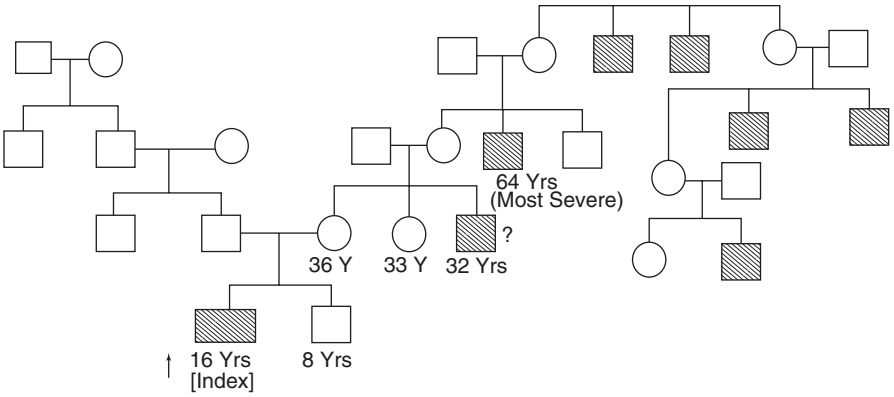

Fig. 39.1 Pedigree chart demonstrating affection of all male members on the maternal side

39.9 Case Study

Clinical details: An 18-year-old boy was brought by his parents for not being good at sports activities at school and being 'clumsy'. The patient himself had very few complaints and mentioned only about toe aches on exertion and not enjoying physical activities. He remembered an occasional fall due to tripping. On coaxing, he revealed slippage of footwear and curling of toes. He had no sensory or sphincter symptoms. He had no weakness in upper limbs and these complain were gradually progressive. Examination showed pes cavus, hammer toes and mildly thickened peripheral nerves. He had weakness of distal hand and feet muscles, and there was sensory loss in a glove and stocking manner up to mid shin and wrists. All deep tendon reflexes were absent. There was a strong family history as shown in pedigree chart where males were affected on the maternal sides over three generations favouring possibility of X-linked transmission (Fig. 39.1).

Electrophysiology revealed absent SNAPs in lower limbs, while SNAPs in upper limbs were attenuated and had prolonged latency. There was prolonged latency and increase in duration of CMAPs along with conduction slowing, prolonged F waves and mild temporal dispersion of varying intensity in nerves of both upper and lower limbs. There was no conduction block. Hence, there was evidence of widespread, multifocal, predominantly demyelinating neuropathy with secondary axon loss.

Summary: An 18-year-old boy presented with X-linked, multifocal, demyelinating sensory motor neuropathy with foot deformities.

Discussion: Genetic evaluation showed a pathogenic amino acid change at DNA position c.64C > G (p.R22G) in the GJB1 gene on chromosome X. Final diagnosis of CMT X was considered.

How is CMT X different from other CMTs?

- X-linked.
- Presence of multifocal demyelination and non-uniform slowing makes it necessary to differentiate from acquired demyelination.
- Transient CNS involvement, e.g. aphasia, ataxia, confusion and pseudobulbar syndrome.
- MRI brain may show white matter changes.

Key Points

When to suspect

- X-linked transmission
- Distal motor dominant neuropathy
- Transient or fixed central nervous system features in some patients

How to investigate

- Electrophysiology may show non-uniform demyelination.
- MRI abnormalities.
- Genetics.

How to treat

- Supportive measures

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Other Inherited Neuropathies I

40

40.1 Introduction

Inherited neuropathies consist of a large group of conditions, and earlier chapters have discussed the common and the best known inherited neuropathies like CMT1, CMT2, CMTX and HNPP. Many other inherited neuropathies which are encountered infrequently are discussed in this chapter. Some of these inherited neuropathies affect both the central and peripheral nervous systems or form parts of syndromes and, in some cases, other organ systems. In such patients, symptoms related to the peripheral neuropathy may be overshadowed by other manifestations of the disease. This topic will provide an overview of the inherited neuropathies listed in Table 40.1. As this is a very large group, the chapter is divided in two parts; part 1 will cover hereditary metabolic disorders, leukodystrophies and hereditary ataxias. Part 2 will deal with mitochondriopathies, hereditary sensory autonomic neuropathy, giant axonal neuropathy and primary erythromelalgia.

40.2 Epidemiology

These neuropathic conditions are uncommon, and information on incidence and prevalence is limited. Familial amyloid neuropathy is prevalent in select populations. Andrade first described FAP in North Portugal in 1952. The disease was subsequently reported in Japan (1968) and Sweden (1976), and case reports are available from most regions. Tangier's disease is named after Tangier Island, Virginia, the origin of the first described cases. The concept of mitochondrial disorder was first introduced in 1962 by Luft et al., and the term mitochondrial encephalomyopathy was first used in 1977 by Shapira to describe cases with complex multisystem diseases with structurally and/or functionally abnormal mitochondria in the brain or muscles. The discovery in 1988 of pathogenetic mutations

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Table 40.1 Classification of other inherited neuropathies

Neuropathies secondary to inherited metabolic disorders • Familial amyloid polyneuropathy (FAP) • Fabry's disease • Refsum's disease • Tangier's disease • Abetalipoproteinaemia • Cerebrotendinous xanthomatosis
Neuropathies associated with leukodystrophies • Metachromatic leukodystrophy • Krabbe's disease • Adrenomyeloneuropathy • Pelizaeus–Merzbacher disease
Neuropathies associated with hereditary ataxias • Friedrich's ataxia • Subtypes of spinocerebellar ataxias • AOA1 and 2 • Ataxia telangiectasia
Neuropathies associated with mitochondrial disorders • Mitochondrial myopathy, lactic acidosis and stroke-like episodes (MELAS) • Myoclonic epilepsy, ragged red fibres (MERRF) • Neuropathy, ataxia, retinitis pigmentosa (NARP) • Mitochondrial neurogastrointestinal encephalopathy (MNGIE) • Sensory ataxic neuropathy with dysarthria and ophthalmoparesis (SANDO) • Leigh's disease
Hereditary sensory and autonomic neuropathies (HSAN)
Hereditary neuralgic amyotrophy
Giant axonal neuropathy
Primary erythromelalgia

in mitochondrial DNA (mtDNA) in Leber hereditary optic neuropathy (LHON) and in Kearns–Sayre syndrome (KSS) revolutionized the diagnosis of mitochondrial disorders. There is a paucity of literature from India as regards these neuropathies. A study of 40 cases of peripheral neuropathy in metachromatic leukodystrophy from South India documented the high degree of consanguinity associated with MLD in India, the existence of MLD with normal serum concentrations of ASA, deposition of orthochromatic lipids and electrophysiological evidence of partial conduction blocks (Bindu et al. 2005). A clinical and histological study of 60 patients of mitochondriopathies from South India showed that the most common clinical syndrome associated with ragged red fibres on muscle biopsy was progressive external ophthalmoplegia (PEO) with or without other signs (Challa et al. 2004). Spinocerebellar ataxias are common in Indian subcontinent, and SCA 1, 2 and 3 are frequently encountered (Wadia and Khadilkar 2014).

40.3 Neuropathies Secondary to Inherited Metabolic Disorders

40.3.1 Familial Amyloid Polyneuropathy (FAP)

It is a life-threatening multisystem disorder resulting from deposition of amyloid in the nerve. There are three main types of FAP based on the precursor protein of amyloid: transthyretin (TTR), apolipoprotein A-1 and gelsolin. The main clinical features and pathogenesis are encapsulated in Tables 40.2 and 40.3 (Planté-Bordeneuve and Said 2011).

40.3.2 Other Inherited Metabolic Disorders

The key clinical features and pathogenesis of conditions in this large group have been enlisted in Tables 40.4 and 40.5.

40.4 Neuropathies Associated with Leukodystrophies

Leukodystrophies are inherited abnormalities of myelin metabolism that affect both the central and peripheral nervous systems. As a group, the central nervous system involvement is dominant, and peripheral neuropathy forms a part of the syndrome. Tables 40.6 and 40.7 provide salient points of clinical presentation and pathophysiology (Costello et al. 2009).

Table 40.2 Clinical features of FAP

Type Of FAP	Onset	Key clinical features
Type I/transthyretin	Early onset: third to fourth decade	Endemic in Portugal, Sweden and Japan. Length-dependent small fibre sensorimotor polyneuropathy with life-threatening autonomic dysfunction. Frequent cardiac and eye involvement
Type II/transthyretin	Late onset: sixth to eighth decade	Restricted form, present with CTS and slowly progresses to peripheral polyneuropathy. Autonomic manifestations are also less prominent
Type III/ apolipoprotein A-1	Fourth to fifth decade	Kidneys, liver and gastrointestinal tract affected, often leading to organ failure
Type IIV/gelsolin	Third to fourth decade	Corneal lattice dystrophy, cranial neuropathy and cutis laxa

Table 40.3 Pathogenesis of FAP

FAP	Inheritance	Gene	Protein
Type I/II	AD	Val30Met	Transthyretin (TTR)
Type III	AD	APOA1 gene	Apolipoprotein A1
Type IIV	AD	Nucleotide 654A in gelsolin gene	Gelsolin

Table 40.4 Key clinical features of inherited metabolic disorders

Diseases	Key clinical features
Fabry's disease	Occurs in males, renal involvement; deafness; angiokeratomas over the trunk and scrotum (Fig. 40.1); painful paresthesias and young stroke; painful small fibre neuropathy (Tuttolomondo et al. 2013)
Refsum's disease	Relapsing remitting or progressive course distal sensorimotor neuropathy, retinitis pigmentosa, hypertrophic neuropathy, cerebellar signs, short fourth metatarsals, sensorineural hearing loss, anosmia, cardiomyopathy and ichthyosis (Wanders et al. 2015)
Tangier's disease	Two types of neuropathy: (1) progressive symmetrical neuropathy involving upper limbs with facial weakness and dissociated loss of pain and temperature. (2) Relapsing multifocal mononeuropathies Enlarged orange tonsils
Abetalipoproteinaemia/ Bassen–Kornzweig syndrome	Fat malabsorption causing severe deficiency of the fat-soluble vitamins, retinitis pigmentosa, peripheral neuropathy and spinocerebellar degeneration with gait ataxia, areflexia, impaired proprioceptive sensations and distal weakness (Zamel et al. 2008)
Cerebrotendinous xanthomatosis	Neurological: ataxia, dystonia, dementia, epilepsy, psychiatric disorders, peripheral neuropathy and myopathy. Non-neurologic: tendon xanthomas, childhood-onset cataracts, infantile-onset diarrhoea, premature atherosclerosis, osteoporosis and respiratory insufficiency (Nie et al. 2014)

Table 40.5 Pathophysiology of inherited metabolic disorders

Disease	Inheritance	Pathogenesis
Fabry's disease	X linked	Deficiency of the lysosomal enzyme α-galactosidase A causing accumulation of the glycolipid globotriaosylceramide
Refsum's disease	AR	Defect in enzyme phytanoyl-CoA-hydroxylase leading to phytanic acid accumulation in serum and tissues PHYH or PEX7 mutation
Tangier's disease	AR	ABCA-1 transporter deficiency and disrupted reverse cholesterol transport resulting in the deposition of cholesterol esters in peripheral nerves and reticuloendothelial system (Puntoni et al. 2012)
Abetalipoproteinaemia	AR	Gene defects coding for the microsomal triglyceride transfer protein, resulting in abnormal very-low-density lipoprotein secretion
Cerebrotendinous Xanthomatosis	AR	Mutations in the CYP27A1 gene which encodes mitochondrial enzyme 27-sterol hydroxylase resulting in decrease of bile acid synthesis and increased cholestanol in plasma and tissues (Preiss et al. 2014)

PHYH Phytanoyl-CoA hydroxylase, *PEX7* peroxisomal biogenesis factor 7, A*BCA-1* adenotriphosphate binding cassette transporter A-1, *CYP27A1* sterol 27-hydroxylase gene

Table 40.6 Key clinical features of neuropathies associated with leukodystrophies

Diseases	Key clinical features
Metachromatic leukodystrophy	Late infantile (6 months–2 years), juvenile (3–16 years): peripheral neuropathy precedes CNS involvement Adult onset: behavioural changes, psychosis, progressive dementia, pyramidal signs, ataxia predominate over neuropathy
Krabbe's disease/globoid cell leukodystrophy	Infantile: hyperirritability, spasticity, fever and developmental arrest Early onset: progressive cognitive decline, spasticity, opisthotonic posture, optic atrophy and seizures Late onset: peripheral neuropathy, spasticity, seizures
Adrenomyeloneuropathy	Psychiatric features, adrenal insufficiency, pigmentation (Fig. 40.2), progressive myelopathy and peripheral neuropathy
SOX10 related disorder	Present in the first year of life with developmental delay and hypotonia with or without peripheral neuropathy. Includes group of disorders characterized by peripheral neuropathy, central hypomyelination, Waardenburg syndrome and Hirschsprung disease (Inoue et al. 2002)

SOX10 SRY-related HMG-box 10

Table 40.7 Pathophysiology of neuropathies associated with leukodystrophies (Osterman et al. 2012)

Disease	Inheritance	Mutated gene	Pathogenesis
Metachromatic leukodystrophy	AR	*ARSA*	ASA gene mutation causing deficiency of the lysosomal enzyme and arylsulfatase A (ASA) and subsequent accumulation of sulfatides in the brain, peripheral nerves and other tissues (Barboura et al. 2010)
Krabbe's disease	AR	GALC	Deficiency of the lysosomal enzyme galactocerebroside β-galactosidase
Adrenomyeloneuropathy	X linked	ABCD1	Defect in beta oxidation of very long-chain fatty acids causing their accumulation
Sox 10 related disorder		SOX10	Transcription factor important for neural crest and glial development

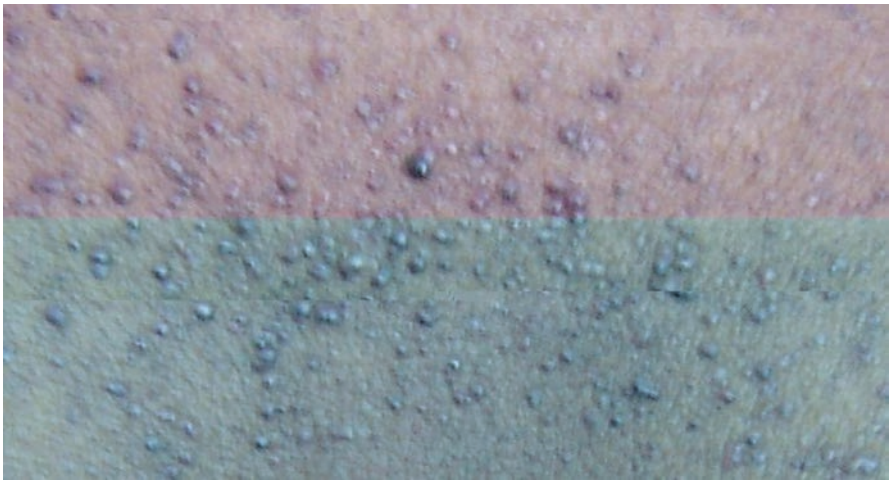

Fig. 40.1 Angiokeratomas in a patient with Fabry's disease

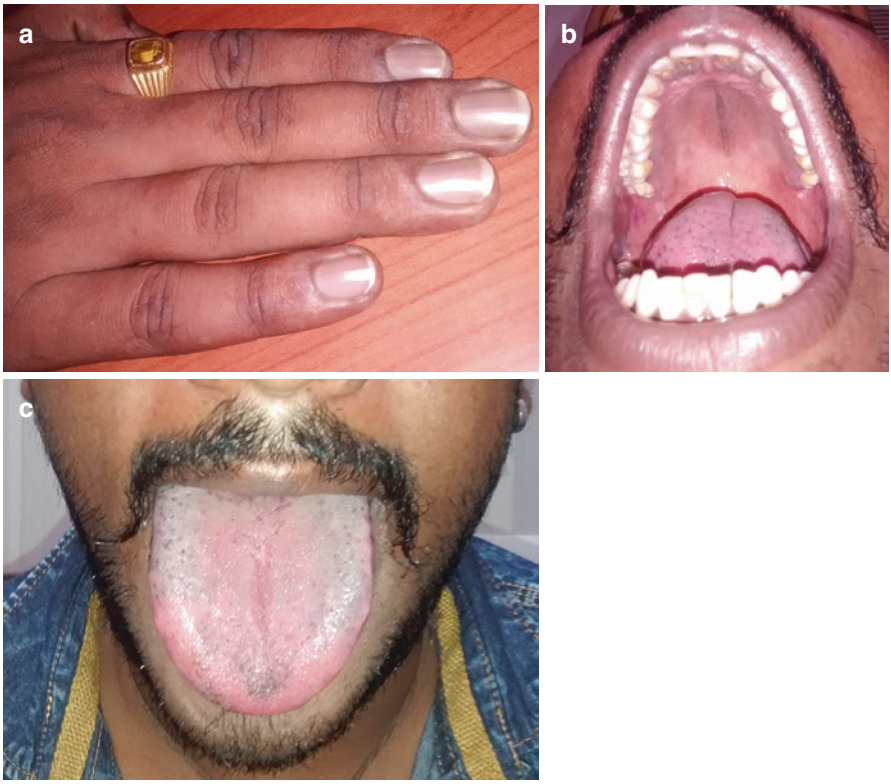

Fig. 40.2 Dark pigmentation over the knuckles (**a**), palate (**b**) and face and tongue (**c**) in a patient with AMN (Courtesy: Dr. Vibhor Pardasani, Bombay Hospital, Mumbai)

40.5 Neuropathies Associated with Hereditary Ataxias

The hereditary ataxias are a heterogeneous group of inherited disorders with varying neuropathological profiles. Most autosomal recessive ataxias manifest early (<20 years), and neuropathy is more common in autosomal recessive ataxias (Fogel and Perlman 2007). Autosomal dominant spinocerebellar ataxias have different combinations of cerebellar and brainstem dysfunction, and peripheral neuropathy is described in some of them. The key clinical features and pathogenesis are tabulated below (Tables 40.8 and 40.9).

Table 40.8 Key clinical features of neuropathies associated with hereditary ataxias

Disease	Key clinical features
Friedreich's ataxia (FA)	Hyporeflexia, extensor Babinski responses, sensory loss, cardiomyopathy, skeletal abnormality
Spinocerebellar ataxia (SCA) subtypes	Cerebellar syndrome with other clinical features SCA1: sensory neuropathy, UMN signs, cognitive decline, ophthalmoparesis SCA2: Slow saccades, neuropathy (Wadia 1984) SCA3: Brainstem signs, neuropathy, UMN, cognitive decline, association with ALS SCA4: sensorimotor axonal neuropathy SCA7: Pigmentary retinopathy, deafness, sensory neuropathy (Salas-Vargas et al. 2015) SCA18: sensory neuropathy, weakness and atrophy, deafness SCA25: sensory neuropathy, GI features
Ataxia with oculomotor apraxia (AOA) 1 and 2	**AOA1**: onset in first decade, sensorimotor neuropathy, nystagmus and oculomotor apraxia, extrapyramidal signs, mild cognitive decline **AOA2**: age at onset in beginning of second decade, lesser degrees of oculomotor apraxia, extrapyramidal signs or cognitive change
Ataxia telangiectasia (AT)	Begins by age 2–3 years, oculomotor apraxia, oculocutaneous telangiectasias, immunodeficiency, radiosensitivity, increased risk for various cancers (especially leukaemia or lymphoma)
Autosomal recessive spastic ataxia of Charlevoix–Saguenay	Spasticity with peripheral neuropathy, amyotrophy

Table 40.9 Pathogenesis of neuropathies associated with hereditary ataxias (Fogel and Perlman 2007)

Disease	Inheritance	Mutated gene	Locus
Friedrich's ataxia	AR	Frataxin GAA triplet repeat expansion	9q13-q21.1
SCA subtypes SCA2, SCA3, SCA1, SCA4, SCA7, SCA25, SCA18 (Akbar and Ashizawa 2015)	.Ad	ATXN gene SCA1–3,7: CAG expansion SCA4,818,25-unknown	SCA1:6p22, SCA2: 12q24, SCA: 14q 32, SCA4: 16q24, SCA7: 3p14, SCA18;7q22-q32, SCA25:2p21-p15
AOA1 and 2	AR	AOA1: Aprataxin AOA2: Senataxin	
Ataxia telangiectasia	AR	ATM	11q22–23.
Autosomal recessive spastic ataxia of Charlevoix–Saguenay	AR	SACS gene–sacsin	13

40.6 Investigations

Key investigations that can be helpful in sorting out inherited neuropathies are tabulated below (Tables 40.10 and 40.11).

Table 40.10 Key investigations in inherited neuropathies

Disease	Electrodiagnosis	Nerve biopsy	Other investigations
Familial amyloid polyneuropathy	Distal axonal neuropathy that affects sensory fibres earlier and more prominently than motor fibres	DNA testing to confirm amyloidogenic *TTR* mutation	Echocardiography to detect cardiac enlargement due to amyloid deposition, renal function tests
Fabry's disease	Small fibre neuropathy	Deposition of glycolipid in small neurons of sensory and peripheral autonomic ganglia, selective loss of small myelinated and unmyelinated fibres in sural nerve	α-galactosidase assay in leukocyte preparations or skin fibroblasts
Refsum's disease	Motor conduction velocities are markedly slowed, and SNAPs are reduced or absent	Hypertrophic neuropathy with prominent onion bulb formation	CSF: elevated protein >100 mg/dl plasma phytanic acid concentration > 200 μmol/L Molecular genetic testing
Tangier's disease	Absent or low amplitude SNAPs and reduced conduction velocities	Segmental demyelination and remyelination with lipid vacuoles in Schwann cells	Reduced high-density lipoprotein and cholesterol with elevated triglycerides
Abetalipoproteinaemia	Large fibre sensory neuropathy		Hypocholesterolaemia, acanthocytes on peripheral smear
Cerebrotendinous xanthomatosis	Slowed nerve conduction velocities	Demyelination and remyelination, some features of axonal degeneration (Ben Hamida et al. 1991)	↑plasma cholestanol ↓ plasma cholesterol, ↓ CDCA level, ↑CSF cholestanol and apolipoprotein B Brain MRI: cerebellar atrophy, symmetric hyperintensities in the dentate nuclei
Metachromatic leukodystrophy	Marked uniform slowing of nerve conduction Delayed latency of VEP and SSEP	Segmental demyelination and thin myelin sheaths with metachromatic inclusions within Schwann cells and macrophages	Increased urinary sulfatide excretion and abnormal ASA enzyme assays in leukocytes or fibroblasts MRI brain: tigroid pattern
Krabbe's disease	Marked uniform slowing of motor conduction velocities	Segmental demyelination, tubular or crystalloid inclusions within Schwann cells	Galactosylceramide galactosidase in leukocytes MRI brain: focal, asymmetric or symmetric white matter changes

Table 40.10 (continued)

Disease	Electrodiagnosis	Nerve biopsy	Other investigations
Adrenomyeloneuropathy	Low CMAP amplitudes and mildly reduced NCVs	Loss of myelinated fibres, small onion bulbs and curvilinear lamellar lipid inclusions in Schwann cells	Very long-chain fatty acid levels MRI brain: posterior dominant white matter changes with enhancement at the margins
Friedrich's ataxia	SNAPs reduced in amplitudes or absent Motor nerve conduction studies are normal or slightly reduced	A selective loss of large myelinated fibres occurs in the sural nerve	Glucose tolerance test, 2D Echocardiographic changes Cervical cord atrophy
SCA subtypes	Distal sensorimotor axonal neuropathy or primary neuronopathy (Álvarez-Paradelo et al. 2011)		MRI brain: olivopontocerebellar atrophy
AOA1 and 2	Sensorimotor neuropathy		AOA1: cholesterol ↑ Albumin ↓, normal serum α-fetoprotein AOA2: α-fetoprotein ↑ cerebellar vermian atrophy
Ataxia telangiectasia	Sensorimotor neuropathy		High concentrations of serum α-fetoprotein Low IgG, IgA, and IgE and high IgM

40.7 Differential Diagnosis

Differential diagnosis of inherited neurpathies with their key distinguishing features have been mentioned in Table 40.11.

Table 40.11 Differential diagnosis of inherited neuropathies with their key differentiating features

Disease	Key differentiating features
HMSN	Pr Progressive distal muscle weakness with feet and legs most severely affected, hammer toes, pes cavus, depressed deep tendon reflexes
HMN	Primary motor symptoms and a lack of sensory and autonomic symptoms. Progressive weakness and atrophy of the distal muscles
HSAN	Progressive loss of sensation which can lead to hyperkeratosis, chronic ulcers, dystrophic nails, osteomyelitis Distal muscle weakness, depressed reflexes Autonomic dysfunction excessive sweating, gastro-oesophageal reflux, postural hypotension self-mutilation, deafness
HNPP	Most episodes are of sudden onset, painless and provoked by compression, traction or other minor trauma EDX: focal slowing and conduction blocks at compression sites and diffuse reduction of SNAP amplitudes. Sural biopsy: tomacula Usually followed by complete recovery within days or weeks
Toxic neuropathies	History of exposure to toxins. Associated systemic features
Immune neuropathies	Acute or relapsing remitting course, proximal plus distal weakness, sensory symptoms, no skeletal deformity, no family history Investigations: EDX conduction blocks, non-uniform motor NCV slowing. CSF-raised proteins Treatment: response to immunosuppression

40.8 Management

40.8.1 Supportive Management

Life expectancy is not altered in most of the inherited neuropathies. Disability is highly variable and cannot be predicted with any certainty. Management is mainly symptomatic. Ankle weakness and instability can be treated with well-fitting shoes or orthoses which distribute the weight equally and prevent potentially disabling injuries such as sprains or ankle fractures. Neuropathic pain is rarely disturbing and responds to medications commonly used for neuropathic pain such as tricyclic antidepressants or anticonvulsants. Patients should be warned to avoid neurotoxic drugs because of greater susceptibility to agents such as vincristine. In patients suffering from FAP, cardiac pacing, haemodialysis, parenteral nutrition, hydration and elastic stockings may become necessary. Midodrine and fludrocortisone can be instituted for orthostatic hypotension. Genetic counselling, family planning, prenatal diagnosis and psychological concerns must be carefully approached, preferably by a multidisciplinary team including a genetic counsellor.

40.8.2 Surgical Treatment

When foot deformities are disabling, ankle–foot braces or orthopaedic procedures like tendon transfers or lengthening (especially the Achilles tendon), hammer toe correction and release of the plantar fascia are of benefit.

40.8.3 Specific Treatment

Specific treatment is available for some of these diseases (Table 40.12).

40.9 Prognosis

In patients with inherited metabolic diseases, earlier presentations due to severe phenotypes have worse outcome due to refractoriness to treatment, and later presentations tend to be associated with poor outcome due to longer untreated periods. Early and sustained treatment can reduce the potential severity of disease, e.g. high oral doses of combined vitamin A and E (abetalipoproteinaemia), dietary restriction of phytanic acid (Refsum's disease), enzyme replacement (Fabry's disease) and CDCA (CTX). For leukodystrophy sufferers, treatment of presymptomatic and early symptomatic disease (bone marrow or cord blood transplantation) reduces severity of disease and can stabilize neuro-regression in children, but motor function may continue to deteriorate. In the late stages, patients progress into spasticity, frontal release signs, incontinence, a state of akinetic mutism, stupor, coma and untimely death. As

Table 40.12 Specific therapies for inherited neuropathies

Fabry's disease	Enzyme replacement therapy: recombinant α-galactosidase-A replacement (agalsidase beta) before irreversible end organ damage takes place (Eng et al. 2001)
Refsum's disease	Dietary treatment: restricting the exogenous (chlorophyll, dairy products, meat) sources of phytanic acid (<10 mg/day). Avoidance of sudden weight loss. Plasma exchange in critically ill patients
Abetalipoproteinaemia	Dietary fat restriction and high doses of vitamin A (100–400 IU/kg/day) replacement of fat-soluble vitamins
Cerebrotendinous xanthomatosis	Chenodeoxycholic acid (CDCA) (750 mg/d), HMG-CoA reductase inhibitors in combination with CDCA
Metachromatic leukodystrophy	Bone marrow transplantation
Krabbe's disease	Haematopoietic stem cell transplantation
Adrenomyeloneuropathy	Dietary restriction of VLCFA, corticosteroid replacement for adrenal insufficiency, bone marrow transplantation at early stages
Friedrich's ataxia	Idebenone
Chronic cerebellar ataxia (van de Warrenburg et al. 2014)	Riluzole 100 mg/day reduces ataxia symptoms (level B) Varenicline 1 mg twice a day Amantadine 300 mg/day

a group, hereditary ataxias are slowly progressive and compromise the quality of life. Balance and gait training help in maintaining mobility for these patients. The overall prognosis depends on management of involvement of other system like cardiac, DM (FA) recurrent infections (AT) and dyslipidemia (AOA).

Key Points

When to suspect

- Symmetric, sensorimotor neuropathies
- Part of a larger syndrome with other neurological features
- Systemic features

How to investigate

- Electrophysiology
- Specific investigations (Table 40.10)

How to treat

- General supportive care
- Specific therapies (Table 40.12)

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Other Inherited Neuropathies II

41

41.1 Mitochondrial Diseases with Peripheral Neuropathy

Mitochondrial disorders are multisystem diseases, with peripheral neuropathy forming a part of the varied clinical involvements. Peripheral neuropathy is seen in 37% of patients with mitochondrial disorders (Colomer et al. 2000) but is often masked by the other more striking signs and symptoms (Menezes and Ouvrier 2012). Key clinical features of neuropathies associated with mitochondrial disorders (Table 41.1).

41.1.1 Pathogenesis

As can be seen from Table 41.2, mitochondrial dysfunction results from various defects in the energy production.

41.2 Hereditary Sensory Autonomic Neuropathy (HSAN)

HSAN is divided into six subtypes, and the clinical features (Fig. 41.1) and pathogenesis are given below (Tables 41.3 and 41.4).

41.3 Uncommon Inherited Neuropathies

Hereditary neuralgic amyotrophy, giant axonal neuropathy and primary erythromelalgia are some of the uncommon forms of inherited neuropathies. Their main clinical and genetic features are tabulated below (Tables 41.5 and 41.6).

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https://doi.org/10.1007/978-981-10-5361-0_41

Table 41.1 Key clinical features of well-recognised mitochondriopathies

Diseases	Key clinical features
NARP	Onset in infancy or early childhood, retinitis pigmentosa, sensory neuropathy, ataxia, seizures, hearing loss, mental retardation and cognitive deterioration
MILS	Same as NARP but with bilateral necrotizing lesion of basal ganglia with spastic dystonia
KSS	Onset <20 years or >50 years. Triad of progressive external ophthalmoplegia, onset before age of 20 and one of pigmentary retinopathy, cerebellar ataxia, heart block and/or elevated CSF protein >100 mg/dl can also have myopathy
MERFF	Onset in childhood and early adulthood, stimulus-sensitive myoclonic epilepsy with photosensitive myoclonus, ataxia, optic atrophy, pyramidal dysfunction, hearing loss
MELAS	Stroke-like episodes with seizures, intermittent encephalopathy, vomiting, migraine-like headaches, ataxia, cognitive impairment, peripheral neuropathy
MNGIE	Onset in second decade, ptosis, progressive external ophthalmoplegia, severe gastrointestinal dysmotility—episodes of pseudo-obstruction and cachexia, leukoencephalopathy, peripheral neuropathy seen in all patients (Hirano et al. 2004)—they can present with numbness, paraesthesia and burning pain in the feet. Exam—atrophy, areflexia, sensory loss in glove-stocking distribution
LHON	Onset 15–30 years, bilateral acute to subacute visual loss Cardiac arrhythmias, postural tremor, myopathy and movement disorders (Yu-Wai-Man et al. 2009), peripheral neuropathy in 20%, usually subclinical (Gilhuis et al. 2006)
Dominant optic atrophy	Onset first–second decade of life, visual loss, dyschromatopsia, central or paracentral scotomas and optic atrophy. Subclinical peripheral neuropathy
SANDO	Progressive external ophthalmoplegia with sensory ataxia, neuropathy, dysarthria—sensory ataxia due to combination of cerebellar and sensory deficits
Mitochondrial CMT	Hereditary neuropathies, distal weakness and wasting, sensory loss, areflexia and foot deformities. Nerve conduction velocity <=38 m/s in upper limb motor nerves (demyelinating) and >=38 m/s upper limb motor nerves (axonal) Most common—CMT2A CMT + corticospinal tract involvement—CMT5 CMT + optic atrophy—CMT6 (Pareyson et al. 2013)

CMT Charcot–Marie–Tooth neuropathy; *NARP* neuropathy, ataxia and retinitis pigmentosa; *MILS* maternally inherited Leigh's syndrome; *SANDO* sensory ataxia, neuropathy, dysarthria and ophthalmoplegia; *MNGIE* mitochondrial neurogastrointestinal encephalopathy; *MELAS* mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; *MERRF* myoclonus epilepsy with ragged red fibres; *LHON* Leber hereditary optic neuropathy; *KSS* Kearns–Sayre syndrome

Table 41.2 Inheritance and pathogenesis of mitochondriopathies

Disease	Inheritance	Genetic abnormalities
NARP/MILS	Mitochondrial, maternal	Mutation in m.8993 T>G or C in the ATPase 6 subunit gene is associated with NARP, but when the mutant load exceeds 90–95%, the patient's phenotype switches to MILS. Leigh's syndrome is a common clinical outcome of any severe oxidative phosphorylation dysfunction. Leigh's syndrome is the mitochondrial disorder with highest genetic heterogeneity (Finsterer 2008)
KSS	Mitochondrial deletion, sporadic	Single large deletion in the commonly deleted region, large tandem duplication (Tuppen et al. 2010)
MERFF	Mitochondrial, maternal	80% have mutation np-8344A>G of the tRNA gene (Tuppen et al. 2010)
MELAS	Mitochondrial, maternal	80% have mutation 3243A>G of tRNA 10% have mutation 3271 of tRNA
MNGIE	Autosomal recessive	Homozygous and compound heterozygous mutations in TYMP gene, thymidine phosphorylase. Multiple mitochondrial deletions
LHON	Mitochondrial, maternal	95% of patients have these three mutations: nt-G11778A (69%), nt-T14484C (14%) (better chance of recovery), nt-G3460A
Dominant optic atrophy	Autosomal dominant	OPA1 gene defect altering mitochondrial dynamics
SANDO	Autosomal recessive and dominant	POLG1 mutation (autosomal recessive >dominant) C10orf2 (autosomal dominant or recessive)
Mitochondrial CMT	Autosomal dominant or recessive	MFN2 (chromosome 1)—CMT2A (AD or AR), CMT5 (AD), CMT6 (AD) GDAP1 (chromosome 8)—CMT2K (AD or AR), CMT4A (AR), recessive intermediate CMTA (AR) (Pareyson et al. 2013)

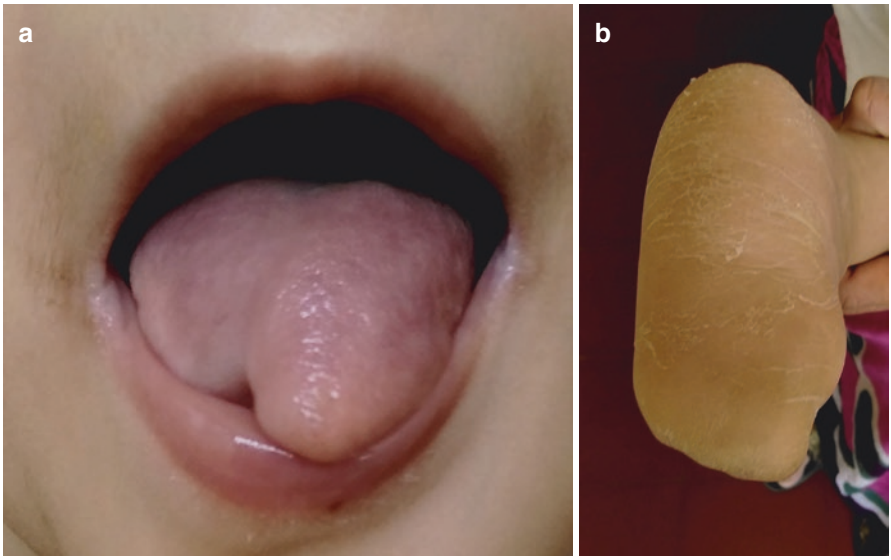


Fig. 41.1 Tongue mutilation (**a**) and foot deformities (**b**) in a patient with HSAN

Table 41.3 Key clinical features of subtypes of HSAN

Types of HSAN	Key clinical features
Type IA/ IB	Sensory loss, acro-dystrophic neuropathy, mild distal weakness, onset in second to fourth decade (Houlden et al. 2006) Type IB—associated with cough and gastro-oesophageal reflux
Type II	Pan-sensory loss in infancy, mild autonomic dysfunction, mental development normal, SNAP absent
Type III	Riley–Day syndrome/familial dysautonomia (FD), begins at birth, sensory loss, absent tears, fungiform tongue papillae, autonomic crises
Type IV	Congenital insensitivity to pain and anhidrosis (CIPA), self-mutilating behaviour, mental retardation, normal SNAPs, absent SSR
Type V	Clinically similar to type IV but no mental disability, normal SNAPs, absent small MF (Houlden et al. 2006)

Table 41.4 Inheritance and genetic abnormalities in HSAN

Disease	Inheritance	Gene	Locus
Type I	AD	SPTLC1	9q22
Type II	AR	WNK1/HSN2	
Type III	AR	KBKAP	9q31
Type IV	AR	NTRK1/NGF receptor	1q21
Type V	AR	NGFB NTRK1/NGF	

Table 41.5 Key clinical features of uncommon forms of inherited neuropathies

Diseases	Key clinical features
Hereditary neuralgic amyotrophy	Severe pain and paresthesia followed by recurrent brachial plexopathy, injury to the upper part of the brachial plexus, dysmorphic features (hypotelorism, epicanthal folds, microstomia and dysmorphic ears) (van Alfen and van Engelen 2006)
Giant axonal neuropathy	Affects PNS and CNS. Characteristic physical appearance is the hallmark (curled red hair, high forehead, pale complexion and long eyelashes), distal leg weakness with peculiar gait (walking on the inner edges of feet) CNS—cerebellar ataxia, optic atrophy, pyramidal signs, cognitive decline
Primary erythromelalgia	Recurrent attacks of pain and erythema of hands and feet in response to warmth and exercise. Recovers with cooling; poor response to pharmacological treatments (McDonnell et al. 2016)

Table 41.6 Important genetic features of uncommon forms of inherited neuropathies

Disease	Inheritance	Gene	Locus
Hereditary neuralgic amyotrophy	AD	SEPT9 gene (Kuhlenbäumer et al. 2005)	17q25
Giant axonal neuropathy	AR	Gan gene, Gigaxonin (Bomont et al. 2000	16q24
Primary erythromelalgia	AD	SCN9A, gain of function mutation of Na(v)1.7	

41.4 Investigations

Table 41.7 depicts the important sets of investigations which can be employed in the diagnosis of the above-mentioned inherited neuropathies.

41.5 Management

Supportive management is on similar lines as described in previous chapter. As a group, mitochondrial disorders benefit by supplements of vitamins and cofactors, antioxidants (coenzyme Q10, idebenone, vitamin C, vitamin E),

Table 41.7 Important investigations

Disease	Electrodiagnosis	Nerve biopsy	Other investigations
Leigh's syndrome (subacute necrotizing encephalopathy)	Axonal neuropathy	Active Wallerian degeneration of both myelinated and unmyelinated fibres	MRI—T2 hyperintensities, most commonly in caudate, putamen and also in thalamus, red nucleus, tegmentum and dentate nucleus (Saneto et al. 2008)
KSS	Axonal neuropathy		Heart block, CSF protein >100 mg/dl
MERFF	Axonal >mixed neuropathy		MRI—stroke-like episodes involve the cerebral cortex, spare white matter and predominantly involve parieto-occipital cortices
MNGIE	Demyelinating sensorimotor neuropathy	Lost or markedly attenuated myelin sheath	MRI—diffuse white matter hyperintensities in cerebral hemispheres
LHON	Demyelinating neuropathy (Gilhuis et al. 2006)		
Dominant optic atrophy	Axonal sensorimotor neuropathy (Yu-Wai-Man and Griffiths 2010)		
Giant axonal neuropathy	Axonal sensorimotor neuropathy	Sural nerve biopsy—large focal axonal swellings with densely packed disorganized neurofilaments	MRI of the brain demonstrates cerebellar and cerebral white matter abnormalities. Electroencephalograms, visual evoked potentials and somatosensory evoked responses are also abnormal
Primary erythromelalgia	Small fibre neuropathy		
Hereditary neuralgic amyotrophy	Painful brachial plexopathy or isolated unilateral nerve palsy		MRI of the plexus, showing thickened and hyperintense nerves

Table 41.8 Specific therapies

Primary erythromelalgia	Cooling of extremity, incomplete response to carbamazepine, tricyclic antidepressants, acetylsalicylic acid
Familial amyloid polyneuropathy	Liver transplantation (<50 years, mild neuropathy (walking unaided), no significant cardiac or renal involvement) Medical treatment—diflunisal (NCT00294671), tafamidis meglumine (NCT01435655)
LHON	Early and prolonged treatment with idebenone improves chances of visual recovery (Klopstock et al. 2013)
KSS	Eyelid props or eyelid surgery, pacemaker for AV block
MELAS	L-arginine may be a promising treatment for stroke-like episodes (Pfeffer et al. 2012). Patients can worsen with dichloroacetate (Kaufmann et al. 2006)
MNGIE	Platelet infusion transiently restores circulating thymidine phosphorylase (Hirano et al. 2012). Allogeneic bone marrow transplantation can have sustained biochemical and clinical improvement (Hirano et al. 2006)

respiratory chain cofactors (thiamine, riboflavin, coenzyme Q10) and compounds that correct secondary biochemical deficiencies (creatine, carnitine) or improve lactic acidosis (dichloroacetate). These specific therapies are summarised in Table 41.8.

41.6 Prognosis

Deficits in hereditary neuralgic amyotrophy tend to recover over weeks to a few months, with accumulating residual neurologic deficit over time. Giant axonal neuropathy begins in early childhood and leads to death by late adolescence. Pain of primary erythromelalgia may lead to significant disability. Patients function normally between episodes. In mitochondrial diseases, the prognosis depends on type of disease. Early diagnosis and treatment of diabetes mellitus, cardiac pacing, ptosis correction, intraocular lens replacement for cataracts and cochlear implantation for sensorineural hearing loss reduce morbidity and mortality.

41.7 Case Study

Clinical details: An 8-year-old girl born out of consanguineous marriage, with uneventful perinatal period and normal personal, social and language development but delayed motor milestone, presented with 4-year history of gradually progressive thinning of the distal lower limb and subsequently involved the proximal lower limb followed by the distal upper limb. Initially able to do so with the support of the floor. Since last 1 year she also had difficulty in getting up from squatting position, initially able to do with support of floor but since last 1 year she took support

of floor followed by knee. She also had difficulty in climbing upstairs as well downstairs. Since 4 years, she used to walk on inner edges of the feet. Since 3 years, she had difficulty in lifting heavy objects with both hands like a glass full of water. She did not have difficulty in combing and turning in bed, double vision, drooping of eyelids, speech changes, paraesthesia, contracture or fluctuation in symptoms. Her younger brother had similar complains since 1 year, like thinning of the distal lower limb, needing support of the floor while getting up from squatting position and walking on inner edges of the feet (Fig. 41.1). Other family members were normal. On examination, there were tightly curled hair, ulnar deviated hands and inverted feet (Fig. 41.1). Her younger brother had similar tightly curled hair, but other family members' hair was not curled (Fig. 41.1). Higher mental functions and cranial nerves were normal. There was non-fatigable nystagmus beating in all directions away from midline. She had generalized hypotonia and normal power in proximal upper limb muscles with weakness of intrinsic hand muscles, hip girdle, knee and ankle joint muscles. There was generalized areflexia with flexor plantar response. Light touch, pinprick and JPS in the upper limb were preserved, while JPS was impaired in lower limbs. Romberg's sign and finger–nose–finger test were positive, while tandem gait was impaired. There were no thickened nerves. On investigation, CK level was 103. Nerve conduction study showed generalized, symmetrical, motor > sensory, lower limb >upper limb and distal > proximal axonal neuropathy. Her younger brother had similar electrophysiological abnormality, while parent's studies were within normal limit. Probable diagnosis of GIANT AXONAL NEUROPATHY was kept in view of characteristic phenotypic features (Fig. 41.2).

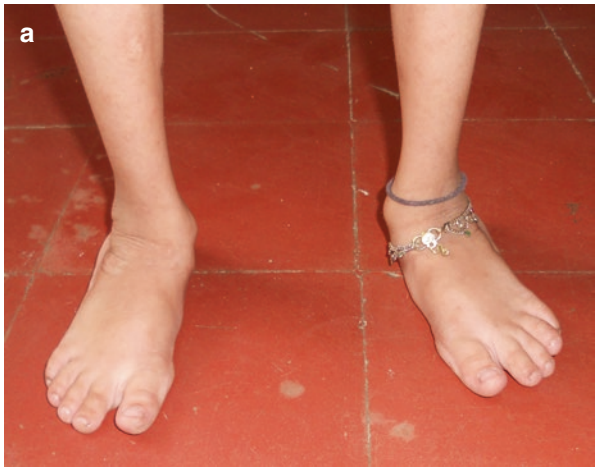
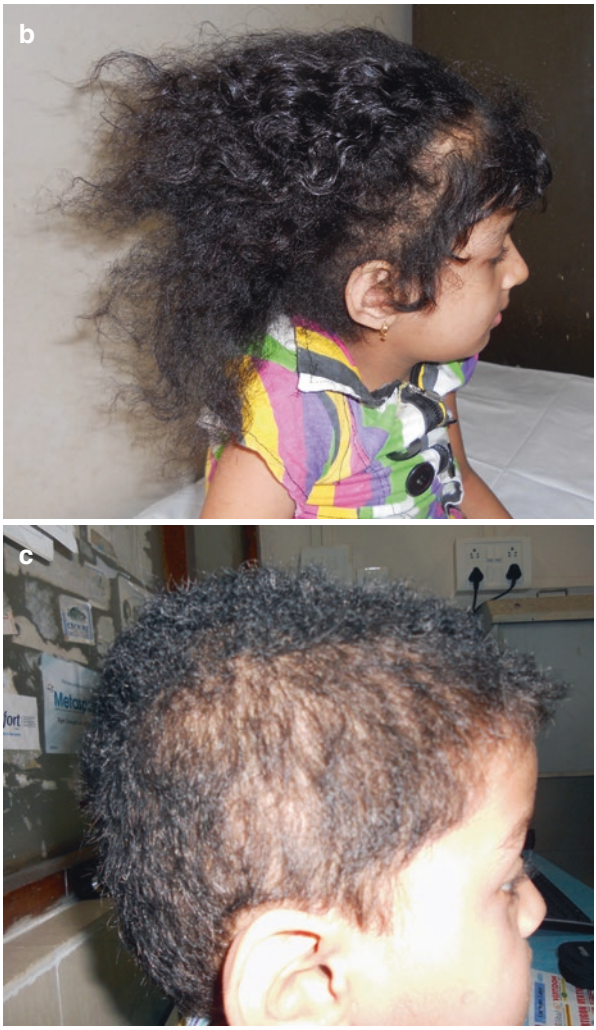


Fig. 41.2 (**a**) Peculiar feet and (**b**) curled hair in patient and (**c**) her younger brother

Fig. 41.2 (continued)



Key Points

When to suspect

- Symmetric, sensorimotor neuropathies
- Part of a larger syndrome with other neurological features
- Systemic features

How to investigate

- Electrophysiology
- Specific investigations

How to treat

- General supportive care
- Specific therapies

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Neuropathies Secondary to Systemic Diseases

42

42.1 Introduction

Various diseases have potential to cause peripheral neuropathy, central nervous system (CNS) involvement and systemic dysfunction. It can occur secondary to metabolic disorders, infections, nutritional deficiencies, toxin ingestion, connective tissue disorders and malignancies. Once a diagnosis of peripheral neuropathy is confirmed, it is important to characterise the type of neuropathy. Clinical presentation depends on the type and portion of fibre affected and gross distribution of nerves affected. The following factors can help to classify neuropathies (Table 42.1).

In addition to characterisation of neuropathy pattern, detection of CNS involvement and systemic features can further help to narrow down the list of differential diagnosis and can have therapeutic implications. This chapter will cover neuropathies secondary to organ dysfunction, metabolic disorders, nutritional deficiencies, infections and toxin ingestion.

42.2 Epidemiology

The exact incidence and prevalence of neuropathies secondary to systemic diseases are not known. Diabetes mellitus (DM), hypothyroidism, vitamin B12 deficiency, chronic renal diseases, human immunodeficiency virus (HIV) and organophosphorus, arsenic and lead intoxication are common diseases that can cause neuropathies.

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Table 42.1 Classification of neuropathies associated with systemic diseases

Classification	Clinical presentation
Sensory fibres	Small fibre: positive sensory symptoms such as tingling, burning, lancinating pain, paresthesias, allodynia, hyperalgesia. Impairment of pain and temperature sensation and foot ulcers are evident on examination. Absence of deep tendon reflexes can occur due to involvement of large fibre component *Large fibre*: negative symptoms such as hypesthesia and sensory ataxia. Hyporeflexia, loss of vibration and joint position sensation and presence of Romberg's sign are found on examination
Motor fibres	Involvement of motor fibres can lead to negative motor symptoms such as weakness, wasting and fatigue and positive motor symptoms such as cramps, myokymia and muscle twitching. Usually distal muscle weakness occurs, but severe cases can lead to proximal weakness
Autonomic fibres	Abnormalities of sweating (hyperhidrosis or anhidrosis), orthostatic hypotension (light-headedness, postural drop of blood pressure), heat and exercise intolerance, impotence, urinary incontinence, early satiety, dryness of eyes and mouth, constipation and trophic and skin colour changes are features of autonomic neuropathy
Demyelinating neuropathy	Length-independent, asymmetric and multifocal involvement of predominant large fibre and motor fibres leads to proximal weakness without atrophy, sensory ataxia and generalised hyporeflexia. It is acute to subacute in onset, and associated cranial nerve involvement can occur in them
Axonal neuropathy	There is length-dependent, symmetric and 'glove-stocking' involvement of sensory and motor fibres. It is slower in onset and more painful and has slower rate of recovery than demyelinating neuropathy. Usually, ankle jerks are depressed, while knee and upper limb reflexes are preserved
Focal neuropathies	Entrapment neuropathies such as median neuropathy at the wrist, ulnar neuropathy at the elbow and radial neuropathy (refer to chapter on individual neuropathies) occur commonly in DM and hypothyroidism. In addition, truncal radiculoneuropathies manifesting as severe truncal pain and truncal muscle weakness and lumbar plexopathy (refer to chapter on lumbosacral plexopathies) can occur in DM. Cranial neuropathies—pupil-sparing third nerve palsy and seventh nerve palsy—can occur in DM. Multiple ocular nerves can be affected in B1 deficiency
Generalised non length-dependent neuropathies	These can present with • Predominant proximal weakness (polyradiculopathy) at the onset similar to GBS or CIDP • Predominantly asymmetric, proximal or patchy sensory affection similar to that in sensory neuronopathies (SNs) • Mononeuritis multiplex (MM) at the onset and may progress to asymmetric polyneuropathy (confluent mononeuritis)
Generalised length-dependent neuropathies	Painful, symmetrical sensory symptoms in the feet at the onset gradually ascend up to calves and thighs and eventually involve the fingertips and hands (DSPN) predominantly due to small fibre involvement. Weakness of toes, ankle dorsiflexors and calf muscles which progresses to cause intrinsic small muscle weakness and large fibre dysfunction can occur in severe cases

DSPN Distal symmetrical sensory polyneuropathy, *GBS* Guillain–Barré syndrome, *CIDP* chronic inflammatory demyelinating polyneuropathy (Alport and Sander 2012)

42.3 Clinical Features and Investigations

42.3.1 Neuropathies Secondary to Metabolic Disorders

Key clinical features and salient investigational findings of neuropathies secondary to metabolic disorders have been summarised below in Table 42.2.

42.3.2 Toxic Neuropathies

Toxic neuropathies occur secondary to exposure to heavy metals, chemicals and medications. Extracting history of exposure to such agents is imperative, when clinical suspicion of toxic neuropathies is strong. Mode of exposure, patterns of neuropathy and other neurological and systemic features of few important toxins are mentioned in Table 42.3.

Ayurvedic medications, which are a traditional system native to India, stress the use of minerals such as lead, arsenic and gold. Hence, history of exposure to Ayurvedic medications is important when heavy metal poisoning is suspected,

Table 42.2 Neuropathies secondary to metabolic disorders

Metabolic disorders	Neuropathy pattern	Other neurological features	Systemic features	Diagnostic tests
DM	DSPN (A) is most common. Diabetic polyradiculopathy (D), MM (A), autonomic and focal neuropathies (D+A) (Table 42.1) are other forms	Stroke and nonketotic hyperglycaemic hemichorea	Polyuria, polydipsia, weight loss, recurrent skin and urinary infections	FBS, PPBS, glucose challenge test and HbA1c
Hypothyroidism	Focal entrapment neuropathies (D) (Table 42.1), DSPN (A) and delayed relaxation of stretch reflex	Mental slowing, Hashimoto's encephalopathy and myopathy	Weight gain, dryness of skin, poor appetite and cold intolerance	Thyroid function tests
Renal failure	DSPN (A); associated large fibre and motor neuropathy (A); motor predominant polyradiculoneuropathy (D+A) can occur	Encephalopathy, myopathy and seizures can occur	Anaemia, fatigue, oedema, skin changes, osteodystrophy and electrolyte imbalance	Renal function tests
Hepatic failure	DSPN (A); motor and autonomic involvement can occur in severe cases	Encephalopathy and extrapyramidal dysfunction	Fatigue, features of stigmata of liver disease	Liver function tests

D Demyelinating, *A* axonal, *FBS* fasting blood sugar, *PPBS* postprandial blood sugar, *HbA1c* glycosylated haemoglobin

Table 42.3 Clinical and investigational features of toxic neuropathies

Toxins	Mode of exposure	Pattern of neuropathy	Other features	Diagnostic tests
Arsenic	Oral: adulteration with opium, aphrodisiac, contaminated ground water and rodenticide	Painful DSPN (A) is most common; motor deficits in severe cases can occur	Keratosis, Mee's line, hair loss in chronic cases; encephalopathy and GI symptoms in acute intoxication	Arsenic levels in the serum, skin and hair
Lead	Inhalation: automobile exhaust, silver refining and welding	Motor predominant focal neuropathy, e.g. radial is common; DSPN can occur	Encephalopathy, abdominal pain more common in children; Beau's line on gums can be seen	Anaemia, basophilic stippling; lead and d-ALA levels
Thallium	Oral: insecticide and rodenticide used as intentional poison	Acute-onset severe motor sensory neuropathy (A) mimicking GBS	Abdominal pain, diarrhoea and headache are common; hair loss in third week and nail changes are useful sign	Thallium levels in blood and hair
OP	Oral: insecticide, acute—suicidal, chronic—occupational	Severe motor (A) neuropathy (acute exposure), sensorimotor (D+A) neuropathy (chronic exposure)	Pyramidal signs, fasciculations and delirium can occur	Serum AChE levels
Alcohol	Abuse	DSPN (A) is most common; motor (A) in severe cases; autonomic neuropathy and GBS-like illness can occur	Myopathy, optic atrophy, cognitive decline, stigmata of liver disease	
Organic solvent—hexanes, carbon disulphide	Industrial exposure: screen printers, rubber, glue, cement and spray painting	Sensory and motor neuropathy (D in early cases and A in late cases)		Urinary 25 hexane dione levels

GI Gastrointestinal, *d-ALA* delta-aminolevulinic acid, *OP* organophosphates, *AchE* acetylcholinesterase, *D* demyelinating, *A* axonal (Misra and Kalita 2009; Staff and Windebank 2014)

particularly in India (Gunturu et al. 2011). Gold-induced neuropathy causes painful paresthesias and myokymia, but it is extremely uncommon. Some medications that can cause neuropathy are metronidazole, isoniazid, linezolid, nucleoside analogues and chemotherapeutic agents such as vincristine and taxanes [http://neuromuscular.wustl.edu/nother/toxic.htm#gold].

42.3.3 Neuropathies Secondary to Infections

Infections lead to a wide spectrum of neuropathies, which are summarised in Table 42.4.

Few viral infections such as rabies, West Nile and enterovirus can lead to GBS-like acute polyradiculopathy. Neuropathies caused by leprosy have been described in chapter of leprosy.

42.3.4 Neuropathies Secondary to Nutritional Deficiency

Key clinical features and investigations of neuropathies secondary to nutritional deficiencies have been summarised in Table 42.5.

Neuropathies due to bariatric surgery are on the rise. Multiple nutrient deficiencies have been proposed to play a significant role. Patients present with gradually progressive sensorimotor axonal neuropathy, but occasionally acute presentation like GBS can occur (Staff and Windebank 2014; Hammond et al. 2013).

Table 42.4 Salient features of neuropathies secondary to infections

Infections	Pattern of neuropathy	Other features	Diagnostic tests
HIV	DSPN (A); MM (A); GBS- and CIDP (D)-like illness; autonomic neuropathy; focal neuropathies; cranial neuropathies; and lumbosacral polyradiculoplexopathy (A+D)	Myopathy; myelopathy; dementia; recurrent skin and lung infections; meningitis; fever, weight loss and diarrhoea	HIV antibodies in serum
Varicella zoster	Focal neuropathies, e.g. V1 distribution and focal radiculopathies in dermatomal distribution	Old age, DM, HIV, malignancy and immunosuppressive agents are risk factors	
Hepatitis C	MM (A) with prominent pain and sensory symptoms	Skin rash, fever, arthralgias and chronic hepatitis	HCV antibody and liver function tests
CMV	MM (A) and painful polyradiculopathy	Usually occurs with HIV	CSF-PCR for CMV
Diphtheria	GBS (D)-like neuropathy with onset in bulbar muscles. Respiratory weakness and quadriparesis occur in severe cases	Usually occurs in children following fever and sore throat. Myocarditis can occur in severe cases	

CMV Cytomegalovirus, *CSF* cerebrospinal fluid, *PCR* polymerase chain reaction (Gabbai et al. 2013 and http://neuromuscular.wustl.edu/nother/infect.htm)

Table 42.5 Neuropathies secondary to nutritional deficiency

Nutrient	Pattern of neuropathy	Other features	Diagnostic tests
Vitamin B1	DSPN (A) is common; distal muscle weakness (A) in severe cases and GBS (A)-like neuropathy can occur	Ophthalmoparesis, ataxia, nystagmus and encephalopathy are associated manifestations	RBC transketolase levels are helpful
Vitamin B6	DSPN (A) is common; mild distal motor weakness (A) can occur; B6 toxicity leads to SNs	B6 deficiency occurs usually in setting of isoniazid treatment	Pyridoxal phosphate levels in blood
Vitamin B12	Large fibre sensory (A) neuropathy is common; mild distal motor weakness (A) can occur	Myelopathy optic neuropathy, anaemia and neuropsychiatric features	Serum B12, MMA and homocysteine
Vitamin E	Large fibre sensory (A) neuropathy	Features of spinocerebellar dysfunction	Serum alpha-tocopherol level
Copper	Sensorimotor neuropathy (A)	Myelopathy and haematological manifestations	Serum copper level

MMA Methylmalonic acid

42.4 Management and Prognosis

Management of neuropathies due to systemic diseases depends on the underlying aetiology.

Toxic neuropathies tend to progress for some time after stopping the culprit agent. Treatment of acute arsenic toxicity consists of dimercaprol and gastric lavage (Vahidnia et al. 2007). Dimercaptosuccinic acid (DMSA) is the oral agent of choice for lead toxicity. Calcium disodium ethylenediaminetetraacetic acid (EDTA) should be used along with dimercaprol in cases of lead toxicity with encephalopathy as EDTA alone can worsen CNS features [http://www.who.int/selection_medicines/committees/expert/18/applications/4_2_ LeadOralChelators.pdf]. Symptoms of thallium poisoning can be ameliorated with haemodialysis, vitamin B complex supplementation and potassium supplementation (Misra et al. 2003).

Nutrient supplementation (B12, 1 mg weekly for 1 month and then monthly, elemental copper 2 mg per day, vitamin E 50–200 U orally and vitamin B6 50 mg per day) should be administered in appropriate cases (Staff and Windebank 2014).

In diabetic neuropathy, tight glucose control can reverse the symptoms and delay progression of painful polyneuropathy (Rosenberg and Watson 2015).

Amitriptyline, gabapentin, pregabalin and duloxetine are helpful in controlling pain, paresthesias and allodynia that are associated with peripheral neuropathy. Presence of comorbidities and side-effect profile should be considered, prior to selection amongst these agents (Rosenberg and Watson 2015). It is important for clinicians to be aware of these neuropathies due to systemic diseases, as management of these diseases is entirely different and many neuropathies are reversible.

42.5 Case Study

Clinical details: A 30-year-old male presented with history of acute flaccid quadriparesis which developed rapidly within a period of a week. He had pain in the abdomen and diarrhoea 2 days prior to onset of limb weakness. Weakness was associated with severe pain and sensory complaints in limbs. Patient did not have respiratory or bulbar weakness. There was no history of fever or sphincter involvement. On examination, he had symmetrical, severe proximal and distal lower limb more than upper limb weakness and was not able to stand or lift his arms. All deep tendon reflexes were absent. Pain prick and temperature sensations were reduced in glove and stocking pattern. At the time of presentation (1 week into the illness), he did not have any skin rash, hair changes or any systemic features. He did not consume alcohol, Ayurvedic medications, aphrodisiacs or any recreational drugs. He was a contractor by occupation and had no history suggestive of exposure to industrial or occupational toxins.

Summary: A 30-year-old male presented with acute flaccid quadriparesis accompanied with severe abdominal pain, diarrhoea and pain in limbs. But there was no apparent cause of toxin ingestion.

Discussion: Possibilities of GBS, toxic neuropathies and vasculitis neuropathy were considered. Points favouring these illnesses were:

- GBS—acute onset quadriparesis with sensory symptoms, areflexia and sparing bowel/bladder functions. Diarrhoea: *Campylobacter jejuni* infection
- Vasculitic neuropathy—painful limb weakness with prominent sensory complains
- Toxic neuropathy—diarrhoea, abdominal pain preceding acute flaccid and painful quadriparesis

Factors against these illnesses were:

- GBS—diarrhoea and abdominal pain at the onset of illness and accompanying severe pain
- Vasculitic neuropathy—symmetrical, proximal > distal weakness and relatively rapid progression
- Toxic neuropathy—no obvious history suggestive of toxin exposure

This patient was treated as GBS with intravenous immunoglobulin (IVIg) over a period of 5 days in the second week of illness. However, patient did not show any improvement, and pain and weakness persisted. Diarrhoea subsided with symptomatic therapy. Clinical presentation and progression of illness were perplexing. In the third week of illness, the patient developed severe hair loss and nail changes (Fig. 42.1). The presence of abdominal pain, diarrhoea at the onset of illness, hair loss and nail changes in the third week favoured toxic neuropathy, particularly thallium or arsenic. Hair clippings and blood were sent for toxicology screening, and they revealed high amounts of thallium. Final diagnosis of acute thallium poisoning

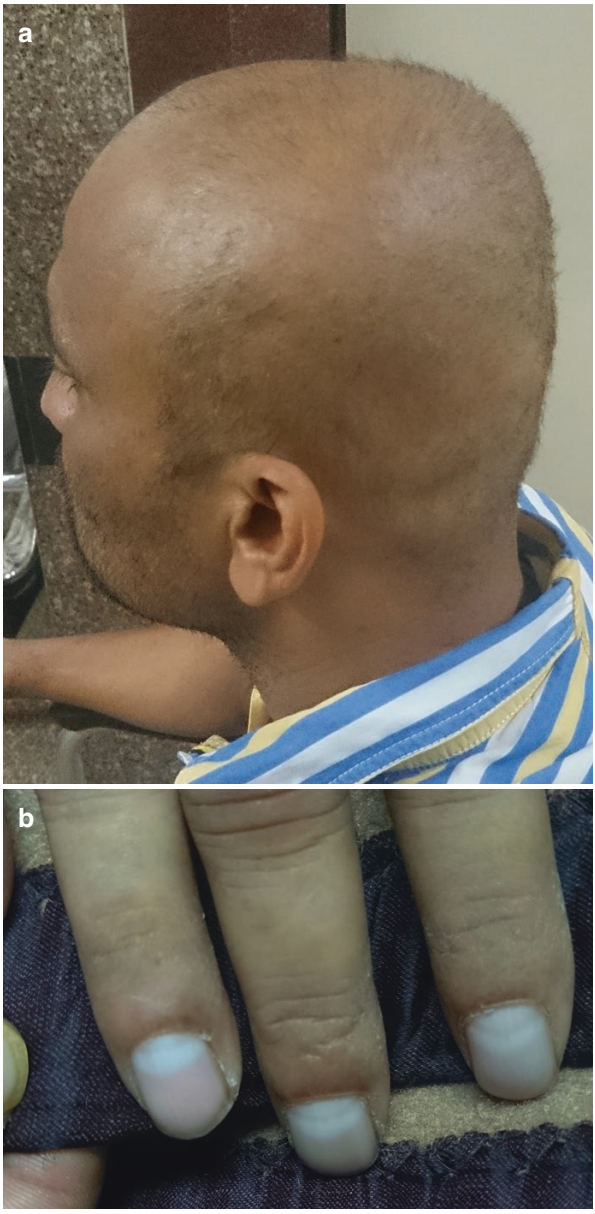

Fig. 42.1 (**a**) Alopecia and (**b**) Mee's lines in a patient with thallium toxicity

was made, and a historical search into the toxin exposure was done. Retrospectively, patient remembered ingestion of a cold drink with his business rivals, prior to onset of illness, which had tested unusual. Whether this drink was spiked with toxin could not be ascertained. This case exemplifies the need for clinicians to appreciate acute

presentations of toxic neuropathies and differentiate it from its mimics, as management and prognosis of these neuropathies are entirely different.

Key Points

When to suspect

- Usually painful sensorimotor neuropathy, occasionally predominant motor features
- Presence of non-neuropathic and systemic features (Tables 42.2–42.5)

How to investigate

- Metabolic survey
- Evaluation of nutrients
- Toxic screen

How to treat

- Treatment of underlying illness
- Avoiding culprit toxins and detoxification therapy
- Supportive therapy

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Porphyrias

43

43.1 Introduction

Porphyrias are a group of inherited metabolic disorders of haem synthesis (Lancet 2010). Enzyme defects in the haem biosynthesis pathway result in the accumulation of haem precursors, e.g. aminolevulinic acid (ALA), porphobilinogen (PBG) and porphyrins. These disorders can present as acute neuro-visceral syndromes, skin lesions or both. Porphyrias are largely transmitted as autosomal dominant disease but, uncommonly, can be recessive. Based on clinical presentation, porphyrias can be classified into acute porphyrias and cutaneous porphyrias. Acute porphyrias present with life-threatening crisis and are most frequently encountered by neurologists. Porphyrias often present with acute quadriparesis, autonomic dysfunction, sensory complaints, abdominal pain and neuropsychiatric manifestations. It is important to screen for porphyrias as delay in treatment can be fatal. This chapter will cover information about porphyrias that present with neurological features (Puy et al. 2010; Solinas and Vajda 2008; Sylantiev et al. 2005). Subtypes of porphyrias that can present with neurological manifestations are mentioned in Table 43.1. Other rare subtypes of porphyrias that can present with neurological features are plumboporphyrias.

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Table 43.1 Porphyrias that present with neurological manifestations

Subtypes of porphyria	Mode of inheritance	Enzyme deficiency	Reaction catalysed	Accumulated products
Acute intermittent porphyria (AIP)	Autosomal dominant	PBG deaminase	PBG to hydroxymethylbilane	PBG and ALA
Hereditary coproporphyria (HCP)	Autosomal dominant	Coproporphyrinogen oxidase	Coproporphyrinogen III to protoporphyrinogen IX	PBG, ALA and coproporphyrins
Variegate porphyria (VP)	Autosomal dominant	Protoporphyrinogen oxidase	Protoporphyrinogen IX to protoporphyrin IX	PBG, ALA, coproporphyrins and protoporphyrins
ALA dehydratase porphyria	Autosomal recessive	ALA dehydratase	ALA to PBG	ALA

43.2 Epidemiology

AIP is the most prevalent form of acute porphyrias and is estimated to occur in 1 in 75,000 people in Europe. It is more common in Sweden, where it is seen in 1 in 1000 people. VP is twice as uncommon as AIP and is particularly common in South Africa. It is estimated to occur at 3/1000 in South African population, and a founder effect has been documented (Schutte et al. 2015; Puy et al. 2010). In the United States, prevalence of disease is 1 in 10–20 thousand populations. From India, case series and case reports of AIP have been reported (Mohanlal et al. 2016; Balwani et al. 2016; Divecha et al. 2016; Patell et al. 2016; Sharma et al. 2012; Kumar et al. 2010). Porphyrias are known to have a higher prevalence amongst some communities in Rajasthan (Bhargava and Gupta 1970; Sachdev et al. 2005; Mundhara et al. 1991). Porphyrias are more common in women than in men. Acute attacks are rare before puberty and after menopause with peak occurrence during the third decade. Rarely, onset in infancy and childhood can occur in autosomal recessive porphyrias (Bylesjo et al. 2009; Andersson et al. 2003).

43.3 Clinical Features

The clinical manifestations of acute porphyrias can range from acute abdominal pain to life-threatening crisis. The most common feature of acute porphyria is abdominal pain. Other manifestations are autonomic dysfunction, dark red (Coca-Cola)-coloured urine (Fig. 43.1), hyponatraemia, sensorimotor peripheral neuropathy and neuropsychiatric features (Kuo et al. 2011; Puy et al. 2010). Cutaneous features occur in VP and HCP but are extremely uncommon in AIP. Clinical features of porphyrias are described in Table 43.2.

Fig. 43.1 Dark urine on exposure to sunlight in a patient with porphyria

43.4 Pathophysiology

In normal individuals, succinyl CoA and glycine are metabolised by ALA synthase (ALAS) enzyme to ALA in mitochondria. ALA enters into haem biosynthesis pathway and is converted to PBG and its derivatives by a series of enzymatic reactions to reach the end product, i.e. haem (Fig. 43.1). In acute porphyria, there is deficiency of these enzymes and accumulation of ALA and its metabolites. ALAS is the rate-limiting enzyme in the biosynthesis of haem. Haem has a direct negative feedback on ALAS, and in porphyria, due to defect in haem biosynthesis pathway, this negative feedback is compromised. In order to increase haem production, ALAS is in disinhibited state, which leads to the increase in synthesis of ALA and its derivatives. Hence, there is accumulation of metabolic products that are upstream to defective enzymes (Fig. 43.2 and Table 43.1). These accumulated products are neurotoxic and thus lead to neuropsychiatric manifestations and neuropathy. Excretion of porphyrins in urine produces dark red discolouration of urine which is its characteristic. Glucose inhibits ALAS activity and thus helps in abortion of acute attack (Albers and Fink 2004; Simon and Herkes 2011; Puy et al. 2010). Acute attacks of porphyria are precipitated by any event that either directly induces ALAS (by inducing cytochrome P450 enzymes) or increases the demand for haem synthesis. These events include hormonal fluctuations, fasting, smoking, infections, alcohol consumption and exposure to porphyrinogenic medications.

Table 43.2 Clinical features of porphyrias

Abdominal pain	Recurrent abdominal pain is the most common presentation of acute attack of porphyria. It can be associated with nausea, vomiting and constipation. It occurs due to autonomic splanchnic neuropathy. Abdominal pain generally precedes development of peripheral neuropathy (Simon and Herkes 2011; Puy et al. 2010). Pains can also be felt in back or thighs
Autonomic neuropathy	Apart from abdominal pain, other features of autonomic dysfunction like tachycardia, hypertension, postural hypotension, diaphoresis and sphincter disturbances commonly occur
Peripheral neuropathy	Peripheral neuropathy builds up few weeks after the onset of abdominal pain. It occurs in 10–40% of patients with porphyria. Neuropathy is typically acute axonal type, predominantly involving proximal muscles, has onset in upper limbs and is associated with cranial nerve palsies and respiratory weakness. Some patients have sensory involvement in glove and stocking distribution (Puy et al. 2010; Simon and Herkes 2011; Albers and Fink 2004). Cases of progressive motor deficits without other autonomic symptoms have been reported (Albertyn et al. 2014). Although porphyrias cause generalised neuropathy, there is selective vulnerability of radial and peroneal nerves (King et al. 2002). Features of chronic neuropathy can develop in patients with ALA dehydratase porphyria in childhood. Affected children tend to manifest psychomotor retardation, ataxia and porencephaly (Puy et al. 2010)
Neuropsychiatric manifestations	At the onset of the acute attack of porphyria, patients have neuropsychiatric features and seizures. Psychiatric manifestations can be mild in form of hypomania, hallucinations and delusions but can be severe like frank psychosis or depression. It is not uncommon to misdiagnose such patients as schizophrenic. Encephalopathy of varying degrees can occur. Patients have irritability at onset, but it can progress to frank delirium. This may be complicated by partial or generalised seizures (Simon and Herkes 2011)
Dermatological features	Cutaneous photosensitivity affecting sun-exposed areas such as back of the hands, face, neck and sometimes on legs and feet. The skin becomes fragile, and negligible trauma leads to skin erosion. In severe cases, bullae and blisters can develop. Hyperpigmentation and hypertrichosis can occur in affected areas
Other features	Presence of dark-coloured urine on exposure to sunlight strongly indicates porphyria (Fig. 43.1). Hyponatraemia occurs in majority of patients and may contribute to encephalopathy and seizures. It is thought to be related to the syndrome of inappropriate antidiuretic hormone (SIADH) but can occur secondary to renal loss. Presence of hyponatraemia and autonomic dysfunction in a patient with acute axonal motor neuropathy points to porphyria (Simon and Herkes 2011)

43.5 Investigations

Investigations in a patient with suspected acute attack of porphyria should be directed to confirm the diagnosis, classify subtypes, detect systemic abnormalities associated with porphyria and rule out close differentials. Characteristic patterns of accumulation of haem precursors are detailed in Table 43.3.

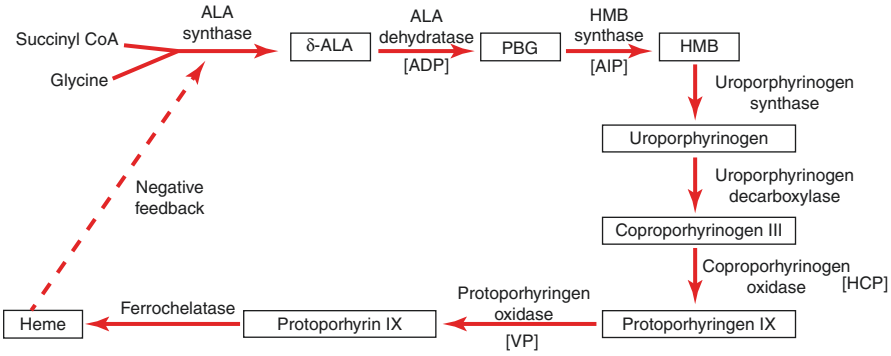

Fig. 43.2 Porphyria pathway

Table 43.3 Patterns of accumulation of haem precursors in acute porphyria

Types of porphyria	Urine ALA	Urine PBG	Urine and stool coproporphyrinogen	Urine and stool protoporphyrinogen
ALA dehydratase deficiency	Elevated	Absent	Absent	Absent
AIP	Elevated	Elevated	Absent	Absent
HCP	Elevated	Elevated	Elevated	Absent
VP	Elevated	Elevated	Mildly elevated	Moderate to severely elevated

Initial screening is done by qualitative rapid urinary PBG testing (Watson–Schwartz test). As this test is not very sensitive, it is followed by quantitative measurements of urinary PBG and ALA levels. Detection of porphyrins can be done in plasma as well. Enzyme abnormalities can be detected in fair number of patients to further delineate porphyria subtypes. DNA analysis for the detection of mutation is gold standard for diagnosis of porphyria and can be used to screen asymptomatic family members (Sharma et al. 2012; Simon and Herkes 2011; Albers and Fink 2004; Puy et al. 2010). Investigations directed to detect systemic abnormalities associated with porphyria are enlisted below in Table 43.4.

Cerebrospinal fluid examination for albuminocytological dissociation and serum lead levels should be done to rule out Guillain–Barré syndrome and lead toxicity.

43.6 Differential Diagnosis

Acute porphyria can mimic various disorders, and management of porphyria is quite unique and challenging. Delay in diagnosis and treatment results in increased morbidity and mortality. Hence, it is important to differentiate acute porphyria from its differentials (Table 43.5).

Table 43.4 Investigations that detect systemic abnormalities of porphyria

Neuroelectrophysiology	Nerve conduction studies (NCS) show acute axonal motor neuropathy affecting proximal muscles of upper limb more than lower limb. There is reduction in motor amplitudes without any changes of conduction block or slowing. These can be asymmetric. NCS may show predominant involvement of radial and peroneal nerves. Electromyogram may show changes of acute denervation during attacks (Albers and Fink 2004; Kumar et al. 2010)
Magnetic resonance imaging (MRI)	MRI brain may show cortical changes consistent with posterior reversible encephalopathy syndrome (PRES) during acute neuropsychiatric presentation. It may be associated with diffuse vasoconstriction of cerebral vessels on angiography. These changes are reversible on subsequent imaging
Blood investigations	Hyponatraemia occurs in majority of patients due to SIADH and vomiting Blood clotting profile needs to be monitored when patients are started on haemin therapy Liver function and renal function tests should be done Creatine kinase (CK) levels and urinary myoglobin to rule out rhabdomyolysis

Table 43.5 Differential diagnosis of acute porphyria with their key distinguishing features

Differential diagnosis	Key distinguishing features
Guillain–Barré syndrome (GBS) – presents with acute quadriparesis, autonomic dysfunction and hyponatraemia	Abdominal pain preceding quadriparesis, recurrent abdominal pain in past, presence of dark-coloured urine on exposure to sunlight, neuropsychiatric features, cutaneous photosensitivity, predominant involvement of proximal upper limbs, absence of CSF albumin-cytological dissociation, absence of demyelinating changes on NCS and presence of urinary PBG and ALA excretion suggest porphyria
Lead toxicity – abdominal pain, motor neuropathy, neuropsychiatric features and elevated urinary ALA levels	Lead neuropathy usually causes neuropathy in adults, while abdominal pain and encephalopathy occur commonly in children. Absence of autonomic features, absence of hyponatraemia during weakness, bluish discoloration of the gums, history of ingestion of Ayurvedic medications or exposure to other known lead sources, elevated urinary PBG and porphyrins, presence of basophilic stippling on peripheral smear suggest lead toxicity
Lambert–Eaton myasthenic syndrome (LEMS)	Subacute onset, predominant lower limb weakness, complaints of fatigue, absence of neuropsychiatric features, characteristic electrophysiological triad, improvement with pyridostigmine or 3,4-DAP favour LEMS
Primary periodic paralysis	Short episodes of weakness lasting up to hours, sparing of facial and respiratory muscles, absence of autonomic dysfunction or neuropsychiatric dysfunction favour periodic paralysis

43.7 Management

Management of acute porphyrias consists of abortion of acute attack, avoiding factors that can precipitate attack and providing symptomatic treatment. Delay in diagnosis and initiating treatment can be fatal and lead to severe neurological deficits. Various therapeutic strategies for porphyrias have been described in Table 43.6:

Table 43.6 Therapeutic strategies for acute porphyria

Abortion of acute attack	Carbohydrates	These inhibit ALAS activity and decreased levels of toxic-accumulated products and thus help to abort acute attack. It can be given orally or through intravenous route. Care should be taken as overzealous administration of hypotonic fluids can worsen hyponatraemia. Vitamin supplementation and monitoring of electrolytes if often necessary
	Intravenous haem administration	Intravenous haem administration is the treatment of choice for acute porphyrias. By replenishing haem stores, the rate-limiting enzyme ALAS is inhibited by a process of negative feedback and inhibits the production of porphyrins. Haem halts further progression of neuropathy but does not reverse established neuropathy. Hence, it should be given early at the onset of illness. Haem is an unstable preparation and has to be given with albumin. Stabilised forms of haem are available as haem arginate and lyophilised haematin. It should be given through a large vein as it can cause thrombophlebitis. Recommended dose of haem arginate is 3–4 mg/kg daily for 4 days and should be administered in normal saline over a period of 30 min. It can cause derangement in coagulation profile, and clotting profile needs to be monitored
	Haemodialysis	In places where haem preparation is not available, haemodialysis can be used for severe illness
Symptomatic treatment	Autonomic neuropathy	Abdominal pain: opioids, paracetamol and aspirin can be used Vomiting: ondansetron, chlorpromazine are safe Constipation: lactulose and laxatives Hypertension and tachycardia: beta blockers, intravenous magnesium sulphate in severe cases Arrhythmias: beta blockers
	Sensorimotor neuropathy	Limb pain: opiates Bulbar weakness: nasogastric tube and speech therapy Respiratory weakness: ventilatory support
	Neuropsychiatric manifestations	Seizures: levetiracetam, clonazepam and gabapentin are safe to use in porphyria Hallucinations: phenothiazines such as chlorpromazine Anxiety and insomnia: clonazepam

(continued)

Table 43.6 (continued)

Prevention of attacks	Avoid porphyrinogenic drugs	Common medications to be avoided in patients with porphyria are enlisted below Antibiotics: isoniazid, rifampicin, pyrazinamide, sulpha drugs and metronidazole Antidiabetics: sulfonylureas Antihypertensives: calcium channel blockers Pain medications: diclofenac Antiepileptics: phenytoin, carbamazepine, phenobarbitone and sodium valproate Oestrogen and progesterone
	Avoid precipitating factors	Avoid smoking, alcohol, fasting and treat infections promptly
Treatment of refractory cases	Liver transplant	Recurrent haemin administration can lead to severe thrombophlebitis and iron overload. Liver transplant can be used in patients with recurrent, severe attacks. Liver transplant returns ALA and porphyrins to normal levels, abolishes attacks and improves quality of life.

Pischik and Kauppinen 2015, Puy et al. 2010, Anderson et al. 2005, Ignacy et al. 1999, Prabahar et al. 2008 and https://www.sps.nhs.uk/articles/how-should-haem-arginate-human-hemin-be-administered-in-the-management-of-acute-porphyria/

43.8 Prognosis

After an initial attack of porphyria, abdominal pain, autonomic symptoms and neuropsychiatric, manifestations rapidly resolve. Recovery from neuropathy is usually slow and produces residual motor deficits. Recurrent and frequent attacks often are associated with fixed weakness and atrophy (Albers and Fink 2004).

Key Points

When to suspect

- Acute quadriparesis, psychiatric features, autonomic features and abdominal pain

How to investigate

- Stand urine to sunlight
- Increased levels of ALA and PBG in urine
- Axonal neuropathy

How to treat

- Glucose
- Acid haematin
- Haemodialysis
- Hepatic transplantation

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Part VIII

Predominant Sensory Syndromes

Sensory Neuronopathies

44

44.1 Introduction

Sensory neuronopathies (SNs) are a rare, heterogeneous subgroup of neuropathies caused by dysfunction of dorsal root ganglia (DRG) and trigeminal ganglion sensory neurons and their central and peripheral sensory projections. The clinical presentation is dominated by negative sensory symptoms such as numbness, gait ataxia and pseudoathetosis due to affection of large fibre neurons. Positive sensory symptoms such as hyperesthesia, burning pain and allodynia can occur if small- and medium-sized neurons are injured. Electrodiagnostic studies show reduction in amplitude of sensory potentials with sparing of motor amplitudes. Multifocal, asymmetrical and predominant upper limb sensory affection helps to differentiate a neuronopathy from the length-dependent axonal neuropathy. It is important to identify SNs, as differential diagnoses are only a handful and many of which are treatable. Causes of SNs are listed in Table 44.1 (Gwathmey 2016; Sghirlanzoni et al. 2005; Camdessanche et al. 2009).

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https://doi.org/10.1007/978-981-10-5361-0_44

Table 44.1 Diseases causing SNs

Paraneoplastic	Small cell lung carcinoma (SCLC), bronchial carcinoma, breast cancer, ovarian cancer, Hodgkin's lymphoma
Immune-mediated	Sjogren's syndrome, systemic lupus erythematosus, celiac disease, autoimmune hepatitis, monoclonal gammopathy
Infectious	Human immunodeficiency virus (HIV), human T-lymphotropic virus (HTLV-1), leprosy, varicella zoster virus (VZV), Epstein–Barr virus (EBV)
Toxic/metabolic	Toxic: Pyridoxine excess, cisplatin, carboplatin, oxaliplatin overdose Metabolic: Niacin, vitamin E and riboflavin deficiency
Hereditary	Sensory ataxic neuropathy with dysarthria and ophthalmoparesis (SANDO); cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS); hereditary sensory autonomic neuropathy (HSAN); hereditary motor–sensory neuropathy (HSMN 2B); Friedreich's ataxia; abetalipoproteinemia and Fabry's disease
Idiopathic	Chronic idiopathic ataxic neuropathy (CIAN)

(Gwathmey 2016; Sghirlanzoni et al. 2005; Khadilkar et al. 2007; Szmulewicz et al. 2015; Camdessanche et al. 2009)

44.2 Epidemiology

The exact incidence, prevalence, age and sex preponderance of SNs are not known. Immune-mediated and paraneoplastic diseases are amongst common causes of SNs. As paraneoplastic syndromes associated with SCLC are more often seen in males and Sjogren's syndrome in females, SNs associated with these diseases tend to follow these sex predilections. In as much as 50% of patients with SNs, the underlying cause cannot be identified.

44.3 Clinical Features

Clinical features of SNs depend on the type of neurons involved. Injury to large fibre neurons results in loss of proprioceptive sensations leading to numbness, sensory ataxia and pseudoathetosis of toes and fingers (Table 44.2). This is the most prominent clinical feature of SNs. Positive sensory symptoms such as burning pain, hyperesthesia and allodynia occur due to affection of small and medium sized neurons, but are less common. Sensory complains tend to be multifocal, asymmetric and can be prominent in upper limbs. Sensory involvement over the face and tongue and nystagmus can be the result of affection of ganglion cells of cranial segments. Deep tendon reflexes are frequently absent. Muscle strength is strikingly normal despite severe sensory loss. Such marked discrepancy between sensory and motor deficits is an indicator towards the anatomical localisation of SN. Difficulties in testing power in the presence of severe incoordination due to deafferentation need to be addressed. Patients often need to visually focus on movement and with visual cues; movements can be performed with normal power. Onset is acute to subacute in onset in paraneoplastic and immune-mediated SNs. Idiopathic SNs tend to have

Table 44.2 Salient clinical features of different causes of SNs

Disease category	Salient clinical features
Paraneoplastic	Presence of pain; concomitant motor neuropathy, autonomic involvement, cerebellar degeneration or limbic encephalitis can be seen; facial involvement is rare
Immune-mediated	*Sjogren's syndrome*: Dry eyes; dry mouth; facial numbness secondary to trigeminal involvement: positive Schirmer's test; hypokalaemic paralysis and renal tubular acidosis *Celiac disease*: Diarrhoea; flatulence; skin rash; weight loss; iron deficiency anaemia; gluten sensitivity; associated cerebellar ataxia
Toxic	*Pyridoxine overdose*: History of ingestion of excess pyridoxine and most patients improve with discontinuation of pyridoxine *Chemotherapeutic agents*: Deficits tend to progress for few months after discontinuation of these agents (coasting effect)
Hereditary	*HSAN*: Small fibre loss, recurrent pain, absence of fungiform papillae, insensitivity to pain *CANVAS*: Cerebellar impairment, vestibular impairment and sensory deficits *Fabry's disease*: Episodic lancinating pains, acroparesthesias, autonomic involvement; angiokeratomas over bathing trunk area; heart, kidney, respiratory tract, cornea, lens, brain vessel involvement *Friedreich's ataxia*: Loss of large sensory neurons, deep sensory loss, spinocerebellar ataxia, cardiomyopathy, diabetes, skeletal deformities
Idiopathic	Indolent, slowly progressive course as compared to immune-mediated or paraneoplastic SNs

indolent course and progression over years. The presence of autonomic dysfunction and motor involvement points towards paraneoplastic neuronopathy (Sheikh and Amato 2010; Gwathmey 2016; Sghirlanzoni et al. 2005).

44.4 Pathophysiology

Dorsal root ganglia contain sensory pseudounipolar neurons which have projections to dorsal horn of spinal cord via dorsal root. These neurons are of two types: large light cells, which receives information from large myelinated fibres (types Ab and Ad for proprioceptive sensations), and the small dark cells, which has connections to small, unmyelinated fibres (type C for small fibre sensations). These cells are second-order neurons that project proprioceptive and tactile sensations through the dorsal column and pain and thermal sensations through spinothalamic tract, respectively. As the capillaries supplying DRG are fenestrated, blood–nerve barrier is loose. This makes DRG susceptible to toxins and antibodies. In paraneoplastic SNs, HuD is main target of autoantibodies. Anti-Hu antibodies trigger a T-cell response which forms main part of pathogenesis of paraneoplastic SNs. Anti-SSA and SSB antibodies, rheumatoid factor (RF), anti-nuclear antibodies (ANA) and Gd1b are frequently detected in immune-mediated SNs. Histological findings show the presence of mononuclear cells and T lymphocytes (Sheikh and Amato 2010; Gwathmey 2016; Sghirlanzoni et al. 2005).

44.5 Investigations

The diagnostic approach in SNs requires a combination of electrophysiological studies, laboratory parameters, cerebrospinal fluid (CSF) analysis, imaging and sometimes tissue biopsy. These parameters are described below:

44.5.1 Electrophysiological Studies

The hallmark of SNs is generalised, asymmetrical, non-length dependent severe reduction in sensory nerve action potential (SNAP) amplitude and preservation of compound motor action potential (CMAP). In some patients, upper limb nerves can be more severely affected than nerves in lower limbs. Needle electrode examination (NEE) may show abnormal spontaneous activity and mild chronic reinnervation in a few patients. Blink reflex abnormalities are more likely to occur in immune-mediated SNs when compared to paraneoplastic SNs (Gwathmey 2016; Camdessanche et al. 2009; Auger et al. 1999).

44.5.2 Laboratory Parameters

Antibodies such as anti-SSA/SSB, ANA, RF, anti-tissue transglutaminase (anti-TTG), anti-dsDNA (anti-double stranded DNA), anti-Hu antibodies and anti-collapsin response mediator protein (anti-CRPM5) should be looked for in patients with SNs. It is important to realise that in 18% of patients with paraneoplastic SNs may have absent antibodies. Hence, clinical and investigative correlation is important for diagnosis of SNs. Virological studies for HIV, HTLV, EBV and VZV can be helpful in selected cases. Toxic screening should be considered in appropriate clinical scenarios (Gwathmey 2016; Molinuevo et al. 1998).

44.5.3 CSF Study

CSF abnormalities such as elevated protein, pleocytosis and oligoclonal bands are more likely to be present in paraneoplastic SNs as compared to other causes (Graus et al. 2001).

44.5.4 Imaging Studies

Magnetic resonance imaging (MRI) studies can help in assessing affection of DRG. DRG degeneration produces increased signal in posterior column, which can be detected on MRI and can be used as an indirect marker of SNs. Recent MRI techniques such as multiple-echo data image combination (MEDIC) can help to demonstrate increased signal intensity in DRG and posterior column in

patients with SNs (Gwathmey 2016; Bao et al. 2013; Sobue et al. 1995). Other imaging modalities such as computed tomography (CT) scan of chest and abdomen and positron emission tomography (PET) scan are presently used as tumour screening tool.

44.5.5 Tissue Biopsy

Biopsy of DRG can demonstrate degeneration of neurons but is not routinely recommended. In a case report, lepra bacilli have been demonstrated on DRG biopsy. Lip and salivary gland biopsy may further support the diagnosis of Sjogren's syndrome. Gastrointestinal (GI) biopsy can be useful to diagnose celiac disease. Biopsy of suspicious mass can be helpful to rule out malignant processes.

44.6 Differential Diagnosis

The list of diseases which present with sensory ataxia is exhaustive. It can be sometimes difficult to differentiate between various causes of sensory ataxia, as some of them have associated areflexia and closely resemble SNs. Differential diagnosis of SNs with their key distinguishing features are discussed in Table 44.3.

Table 44.3 Differential diagnosis of SNs with their key distinguishing features

Differential diagnosis	Key distinguishing features
Chronic immune demyelinating polyradiculopathy (CISP)	Subacute to chronic onset sensory ataxia; loss of proprioceptive sensations in lower limb >upper limbs; usually symmetrical; relatively milder affection of small fibre sensations; normal SNAPs; elevated CSF proteins; hypertrophy and enhancing lumbosacral roots on MRI neurography
Subacute combined degeneration (SACD)	Subacute onset; impairment of large fibre sensations with relative preservation of small fibre sensations; exaggerated knee reflex and absent ankle reflex; inverted V-shaped signal on spinal cord MRI favour SACD
Sensory chronic inflammatory demyelinating polyneuropathy (S-CIDP)	Subacute onset sensory ataxia; loss of proprioceptive sensations in lower limb >upper limbs; usually symmetrical; relatively milder affection of small fibre sensations; elevated CFS proteins point towards sensory CIDP
Axonal neuropathy	Length-dependent small fibre > large fibre impairment; lower limb >upper limb involvement; lesser prominent sensory ataxia; preservation of upper limb reflexes till late into the illness are features of axonal neuropathy
Mononeuritis multiplex	Painful; asymmetrical sensory > motor involvement; distribution follows territories of individual nerves; sensory and motor affection on NCS favour mononeuritis multiplex

For confirmation of diagnosis and differentiation of SN from sensory neuropathy, SN score has been validated (Camdessanche et al. 2009). SN score is calculated as follows:

- Ataxia in the lower or upper limbs at onset or full development: 3.1
- Asymmetrical distribution of sensory loss at onset or full development: 1.7
- Sensory loss not restricted to the lower limbs at full development: 2.0
- At least 1 SNAP absent or 3 SNAP <30% of the lower limit of normal in the upper limbs, not explained by an entrapment neuropathy: 2.8
- Less than two nerves with abnormal motor nerve conduction studies in the lower limbs: 3.1

Possible SN: SN score > 6.5.
Probable SN: SN score > 6.5 and if

- The initial workup does not show biological perturbations or electroneuromyography findings excluding sensory neuronopathy *and*
- The patient has one of the following disorders: onconeural antibodies or a cancer within 5 years, cisplatin treatment, Sjogren's syndrome *or*
- MRI shows high signal in the posterior column of the spinal cord.

Definite SN: If DRG degeneration is pathologically confirmed on biopsy.

44.7 Management

As SNs are uncommon, there is paucity of randomised, controlled trials for treatment of SNs associated with immune-mediated and paraneoplastic disorders. Treatment of acquired SNs is often based on uncontrolled studies and expert opinions (Gross and Johnston 2009; Antoine and Camdessanche 2013). Therapy consists of immunosuppressive agents, discontinuation of toxin and replacement of vitamins and is summarised in Table 44.4.

There are no specific therapies for hereditary and idiopathic SNs at present.

Table 44.4 Management of SNs

Subtypes of SNs	Management
Paraneoplastic	Tumour treatment: Removal of tumour can help in stabilisation of illness Immunomodulatory agents: Intravenous methylprednisolone and/or intravenous immunoglobulin (IVIg) form the first-line management. Monthly pulses of cyclophosphamide can also help in stabilisation of illness Symptomatic treatment: Amitriptyline, duloxetine, gabapentin, pregabalin can be helpful in ameliorating neuropathic pain

Table 44.4 (continued)

Subtypes of SNs	Management
Immune-mediated	Immunomodulatory agents form the main treatment of immune-mediated SNs. Intravenous methylprednisolone, IVIg, monthly cyclophosphamide, azathioprine and rituximab have been used with varying benefits
Toxic/metabolic	Discontinuation of toxic agents like pyridoxine and chemotherapeutic agents and symptomatic treatment are the mainstay of therapy in this subgroup
Infections	Therapy is directed towards underlying infections such as HIV and leprosy

(Attal et al. 2010; Antoine and Camdessanche 2013; Gwathmey 2016)

44.8 Prognosis

Prognosis depends on the underlying aetiology of SNs. Majority of patients with immune-mediated and a smaller proportion of paraneoplastic SNs show significant improvement with immunosuppressive agents. While most of the patients with pyridoxine toxicity have resolution of symptoms after discontinuation of pyridoxine, chemotherapeutic agents exhibit coasting effect and deficit are known to progress for some months. Idiopathic and hereditary SNs progress relentlessly.

44.9 Case Study

Clinical details: A 38-year-old male presented with gradually progressive imbalance while walking, numbness in all four limbs and paresthesias in both feet, which began 1 year before presentation. He had normal speech and had no weakness of upper or lower limbs. On examination, there was pseudoathetosis, sensory ataxia and positive Romberg's sign suggestive of severe proprioceptive loss in both lower and upper limbs. Pain, touch and temperature sensations were largely preserved. All deep tendon reflexes were absent and motor examination was completely normal.

Summary: A 38-year-old male patient presented with severe sensory ataxia with areflexia.

Discussion: Nerve conduction studies showed absent sensory potentials with preservation of motor amplitudes suggestive of DRG pathology. As mentioned in Table 44.2, the presence of associated clinical features can help to differentiate between different causes of ganglionopathy. In 1996, he had developed rash on the flexor aspect of elbow and extensors of the knees (suspected to have dermatitis herpetiformis) along with diarrhoea. GI biopsy was done and celiac disease was diagnosed. He was doing well on dapsone and gluten-free diet till 2014. Cutaneous and GI complaints had subsided, but he presented with ganglionopathy. Hence, anti-TTG was done and was strongly positive. HIV, anti-SSA and anti-SSB were negative. In this case, the important lead to the diagnosis came from the cutaneous lesions and investigations thereof.

Key Points

When to suspect

- Subacute onset, asymmetrical, pain in limbs
- Proprioceptive loss – pseudoathetosis, positive Romberg's sign
- Areflexia
- Preserved motor system

How to investigate

- Absent SNAPs with preservation of CMAPs on NCS
- Systemic markers of immune disease
- Search for neoplasm
- Toxic screen and deficiency states

How to treat

- Immunomodulation
- Tumour removal
- Symptomatic therapy
- Treatment of underlying illness

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Distal Acquired Demyelinating Symmetric Neuropathy

45

45.1 Introduction

Katz et al. (2000) described patients who had mainly distal sensory neuropathy which was symmetrical, resulting in sensory ataxia, and electrophysiologically had a demyelinating pattern in the motor nerves. The authors coined the term distal acquired demyelinating symmetric (DADS). It was later realised that patients with clinical features of DADS tend to have IgM monoclonal gammopathy and antibodies to the myelin-associated glycoprotein (MAG) (Latov et al. 1988; Nobile-Orazio 1998). A proportion of patients do not have the antibodies (Katz et al. 2000; Larue et al. 2011). Presently, those patients who have the antibodies are called as DADS and those who do not are included in DADS variant of CIDP (Joint Task Force of the EFNS and the PNS 2010; Larue et al. 2011). Patients having exclusive increase of IgM Kappa are labelled DADS-M (Katz et al. 2000). 'CIDP-MGUS' and 'IgM MGUS neuropathy' are the alternative names used in the literature for such patients. Patients with the DADS phenotype who do not have an M-protein are designated as idiopathic DADS neuropathy (DADS-I). It needs to be appreciated that there is an overlap between CIDP and DADS, and the distinction gets blurred in patients who do not exhibit the presence of specific antibodies mentioned above (Leitch et al. 2013).

45.2 Clinical Features

45.2.1 DADS-M

DADS-M affects older individuals in their sixth or seventh decades and males outnumber females. The neuropathy is largely sensory and distal. The profound sensory involvement leads to sensory ataxia, gait changes and falls. Motor signs are infrequent and when present are essentially distal in the limbs. Curiously, in this largely sensory phenotype, electrophysiology shows demyelination of the motor nerves.

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45.2.2 DADS-I

DADS-I patients may present at younger ages when compared to DADS-M, and the male predominance is not seen in this group. These patients overlap with the clinical descriptions of 'sensory CIDP' (Oh et al. 1992). In this group as well, electrophysiology shows demyelination of the motor nerves.

45.2.3 Associations

Lymphoproliferative malignancies, colorectal carcinoma (Ayyappan et al. 2015), neuroendocrine tumours (Alam et al. 2017), adalimumab, an antitumour necrosis factor (TNF)-α agent (McGinty et al. 2015) and postvaccination (Gable et al. 2013).

45.3 Investigations

45.3.1 Antibodies

Antibodies against myelin-associated glycoprotein (MAG) are present in majority of patients (Katz et al. 2000). Most patients show elevation of the CSF protein content.

45.3.2 Electrophysiological Study

The main electrophysiological findings are in the motor nerves. Motor NCS show slowing which is largely symmetrical and most prominent in the distal nerve segments. The distal motor latencies are much prolonged and form an important suggestion to the diagnosis of DADS. The prolongation of distal latencies leads to short terminal latency index (TLI) which is highly suggestive of anti-MAG neuropathy (Kaku et al. 1994; Trojaborg et al. 1995). Conduction blocks are uncommon in this form of neuropathy.

45.4 Differential Diagnosis

As the clinical syndrome is of distal sensory symmetrical neuropathy, the wide differential diagnosis of predominantly sensory neuropathies needs to be clinically considered. Demyelinating electrophysiological features and the presence of antibodies help to separate DADS from other neuropathies.

45.5 Management

Immunomodulatory medications have been used in this group of conditions, but the response tends to be far from satisfactory. Judging the response is also fraught with difficulties, as the syndrome is largely sensory. Patients with DADS-M are particularly resistant to therapy measures (Dyck et al. 1991; Nobile-Orazio et al. 2000). As the disabilities are not profound and the response meagre, it is recommended that the use of immunotherapy be judged case by case, on individual merit (Joint Task Force of the EFNS and the PNS 2006). Patients having DADS-I respond better than DADS-M but not as well as the conventional CIDPs.

45.6 Prognosis

The outlook is not as favourable as the conventional CIDP and symptoms continue. However, as the motor system is largely speared, the disabilities are also limited to the sensory system and ambulation is maintained for long intervals (Katz et al. 2000; Saperstein et al. 2001). Patients with DADS without monoclonal gammopathy respond better to immunotherapy in most instances.

Key Points

When to suspect

- Older males.
- Distal sensory ataxic neuropathy.
- Mild motor weakness may be present.

How to investigate

- Electrophysiology: motor conduction blocks
- IgM paraprotein
- MAG antibody

How to treat

- Poor response to IVIg, PE, steroids, cyclophosphamide

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Paraproteinaemic Neuropathy

46

46.1 Introduction

Monoclonal proteins (paraproteins or M protein) are produced by clonal population of B lymphocytes or plasma cells. Monoclonal proteins are common in older population and are characterised by subtype of heavy chains (IgM, IgG, IgA and rarely IgD and IgE) and light chains (kappa or lambda). The clinical spectrum of paraproteinaemic neuropathy (PPN) is heterogeneous and axonal neuropathy, chronic inflammatory demyelinating polyneuropathy (CIDP), distal acquired demyelinating symmetric neuropathy with M protein (DADS-M) or small fibre neuropathy (SFN) (Table 46.1) which are known to occur. PPN can be seen secondary to haematologic disorders like polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS), Waldenstrom macroglobulinaemia, multiple myeloma, cryoglobulinaemia and amyloidosis. For patients in whom the paraproteins are not co-occurring with any haematologic disorder, the condition is termed as monoclonal gammopathy of undetermined significance (MGUS) (Table 46.1). In the presence of paraproteins and neuropathy, it is important to determine the cause–effect relationship, as coexistence is not uncommon. It is important to recognise PPN, as treatment and prognosis of these neuropathies is entirely different from primary CIDP (Cao et al. 2016; Joint Task Force of the EFNS and the PNS 2010; Raheja et al. 2015; Zivković et al. 2009; Mauermann 2014).

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Table 46.1 Clinical patterns of PPN associated with haematologic disorders

Haematologic disorder	Monoclonal proteins	Neuropathy pattern
MGUS	IgM kappa is more frequently associated with neuropathy than IgG or IgA kappa	Predominantly demyelinating neuropathy like DADS-M (50% have anti-MAG antibody) Demyelinating neuropathy like CIDP is more common; axonal neuropathy can occur
POEMS	IgG or IgA lambda	CIDP like illness more common than axonopathy
Amyloidosis	Only light chains lambda >kappa	Axonal sensorimotor neuropathy with autonomic involvement; focal entrapment neuropathies like carpel tunnel syndrome (CTS); SFN
Waldenstrom macroglobulinaemia	IgM kappa	DADS-M (50% have anti-MAG antibody); sensorimotor axonal neuropathy
Multiple myeloma	IgG > IgA; kappa >lambda	Predominantly axonal neuropathy

46.2 Epidemiology

Monoclonal proteins are common, seen in 3.2% of individuals older than 50 years and greater than 5% after 70 years of age. In an experience from tertiary centre, monoclonal proteins commonly co-occur with neuropathy, with an incidence up to 10% in one study (Mauermann 2014). From India, POEMS has been reported to be the most common PPN (Singh et al. 2003; Gupta et al. 2012; Kulkarni et al. 2011). Other reported PPN are MGUS, cryoglobulinaemia and myeloma (Khadilkar et al. 2011; Mehndiratta et al. 2004; Malhotra et al. 2011; Kishore and Misra 2008; Sahota et al. 2005). Disorders like MGUS, POEMS and Waldenstrom macroglobulinaemia show a male preponderance (Mauermann 2014).

46.3 Clinical Features

The clinical spectrum of PPN is wide and includes small fibre neuropathy, sensorimotor axonal polyneuropathy, distal or proximal demyelinating neuropathy and autonomic neuropathy. Features of systemic involvement secondary to haematologic disorders accompany in secondary cases. The clinical features of various PPN are described in Table 46.2.

Table 46.2 Clinical features of PPN

Haematologic disorder	Features of neuropathy	Systemic features
MGUS	Onset in sixth or seventh decade; distal, symmetric demyelinating neuropathy affecting predominantly large fibres leading to sensory ataxia; mild distal weakness can be present	Absence of systemic involvement
POEMS	Fifth or sixth decade onset; distal > proximal; sensory symptoms associated with weakness; areflexia; demyelinating neuropathy can be severe enough to leave patient wheelchair bound	Organomegaly (lymphadenopathy or hepatosplenomegaly); endocrinopathy (diabetes mellitus, hypothyroidism); skin changes (hyperpigmentation, hypertrichosis, sclerosis); clubbing; pedal oedema; papilloedema; ascites
Amyloidosis	Median age at onset is 65 years and rarely before 40 years; painful small fibre involvement in lower limbs with autonomic involvement (orthostatic hypotension, abnormal sweating, bowel and bladder disturbance, early satiety); associated with weakness; entrapment neuropathy like CTS	Signs of renal and cardiac failure; pseudohypertrophy of muscles, e.g. macroglossia; hepatosplenomegaly; bleeding diathesis; Argyll Robertson pupil may occur in a small proportion of patients
Waldenstrom macroglobulinaemia	Seventh decade onset; distal > proximal large fibre involvement; weakness and mild autonomic involvement can occur	Fatigue due to anaemia; hepatosplenomegaly; lymphadenopathy; hyperviscosity related symptoms (epistaxis, shortness of breath, blurred vision and dizziness)
Cryoglobulinaemia	Presents as painful small fibre neuropathy, sensorimotor axonal polyneuropathy or mononeuritis multiplex	Skin rash; purpura; arthralgia; renal involvement
Multiple myeloma	Median age at diagnosis in seventh decade; rarely occurrence before 40 years of age; distal > proximal symmetrical sensorimotor neuropathy; sometime painful small fibre neuropathy; focal entrapment neuropathy, e.g. CTS	Systemic features, e.g. fatigue, weakness, bone pain, weight loss; recurrent infections; features of hypercalcemia and renal failure

(Mauermann 2014; Raheja et al. 2015; Kulkarni et al. 2011; Zivković et al. 2009)

46.4 Pathophysiology

The pathophysiology of PPN mainly revolves around the concept of interaction of antibodies produced by clonal proliferation of plasma cells with specific antigenic targets on peripheral nerves. Antibodies are directed against peripheral nerve glycolipids and glycoproteins like myelin-associated glycoprotein (MAG), cross-reactive glycolipid sulfoglucuronyl paragloboside (SGPG) or gangliosides (GM1, GM2). Pathogenic antibodies consist of isolated heavy chain or light chain or both. IgM antibodies have higher association with neuropathy as compared to IgG antibodies. Levels of IgM may not correlate with severity of illness, but clinical improvement may be associated with fall in antibody levels. IgM antibodies tend to be associated with demyelinating neuropathy, while IgG and IgA antibodies tend to cause axonal damage. Apart from antibodies, deposition of amyloid, immunoglobulins and T-cell infiltration can cause direct toxic effects or indirect nerve damage secondary to vasculopathy (Zivković et al. 2009; Eurelings et al. 2001; Vital 2001; Van den Berg et al. 1996).

46.5 Investigations

Diagnostic evaluation is primarily directed towards detection of a possible haematological malignancy, characterisation of monoclonal protein as well as the underlying neuropathy. Monoclonal proteins are detected by various methods like serum immunofixation electrophoresis (SIFE), serum protein electrophoresis (SPEP), free light chain assay and quantitative immunoglobulins. Systemic involvement can be evaluated by testing for serum calcium, complete blood count (CBC), serum creatinine, skeletal survey for bone lesions, erythrocyte sedimentation rate (ESR) and bone marrow examination for detection of plasma clonal cells. Salient haematological, electrophysiological and systemic investigational findings in various PPN are summarised in Table 46.3.

CSF proteins are elevated in demyelinating PPN and help to differentiate it from axonal neuropathy. Nerve biopsy can be helpful in confirming diagnosis of some types of PPN. Amyloid deposition can be detected by the presence of amorphous material in small endoneurial blood vessels on haematoxylin–eosin staining. The presence of Congo red-positive deposits and apple-green birefringence on polarised light is diagnostic of amyloidosis. Immunostaining of biopsy specimen helps to detect deposition of M protein in endoneurial blood vessels (Zivković et al. 2009; Mauermann 2014; Joint Task Force of the EFNS and the PNS 2010; Raheja et al. 2015).

Table 46.3 Salient investigational findings in various PPN

Haematologic disorder	SIFE or SPEP	Electrophysiological findings	Haematologic and systemic findings
MGUS	IgM kappa or IgG/IgA kappa levels <3gm/dL	Distal, large fibre, demyelinating neuropathy; motor involvement and axonal changes can occur	<10% clonal plasma cells on bone marrow; CBC, creatinine, calcium and skeletal survey are within normal limits; anti-MAG antibody can be present
POEMS	Elevated IgG or IgA lambda levels	Demyelinating > axonal, sensory > motor polyneuropathy	Polycythaemia; thrombocytosis; raised blood sugar; decreased T3,T4 and raised TSH; osteolytic lesions with sclerotic rims; elevated VEGF; raised CSF proteins
Amyloidosis	Free light chains are elevated in serum and urine; lambda > kappa chains	Axonal, sensory > motor neuropathy; abnormal SSR; CTS or other features of entrapment neuropathy	Bone marrow shows clonal plasma cells; restrictive cardiomyopathy on cardiac MRI; biopsies of abdominal fat pad, rectum and of clinically affected organ to detect amyloid deposition
Waldenstrom macroglobulinaemia	IgM kappa levels >3gm/dl	Sensory > motor, axonal neuropathy; demyelinating changes are less common	Anaemia; thrombocytopenia; elevated beta2-microglobulin; bone marrow shows lymphoplasmacytic infiltrate; CT chest and abdomen for lymphadenopathy
Multiple myeloma	IgG kappa is most commonly elevated M protein; levels >3gm/dl seen	Distal > proximal; sensory > motor; axonal neuropathy; rarely demyelination; focal entrapment neuropathy like CTS	Anaemia; hypercalcemia; elevated creatinine levels; raised beta-2 microglobulin; bone marrow biopsy shows >10% plasma clonal cells; osteolytic bony lesions
Cryoglobulinaemia	Presence of cryoglobulins in serum	Axonal neuropathy	Decreased complement C1, C2 and C4 levels; hepatitis C positive; raised ESR and CRP; presence of other autoantibodies like RF

VEGF vascular endothelial growth factor, *TSH* thyroid stimulating hormone, *CSF* cerebrospinal fluid, *SSR* somatosensory response, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *RF* rheumatoid factor

46.6 Differential Diagnosis

An important step early in the differential diagnosis is to establish whether paraprotein is a cause of neuropathy or relationship is mere coincidental. Patients with IgM paraproteins are more likely to be causally related to neuropathy than with IgG or IgA paraproteins. As clinical spectrum of PPN is wide, list of differential diagnosis is substantial. Diseases presenting as SFN, CIDP, axonal neuropathy, autonomic dysfunction and mononeuritis multiplex form close differential of PPN (Table 46.4).

Table 46.4 Differential diagnosis of PPN with their key distinguishing features

Differential diagnosis	Key distinguishing features
Primary CIDP	Presence of features such as time to peak of neuropathy <6 months, relapsing/remitting course, involvement of cranial nerves, asymmetry, history of preceding infection and the presence of IgG/IgA paraproteins without biopsy features favours coincidental existence of paraproteins and neuropathy. MGUS is more common amongst elderly males
Hereditary sensory autonomic neuropathy (HSAN) – present as SFN	Childhood onset; painless ulcers without any skin patches or nerve thickening; minimal sensory complains but profound sensory loss on examination favour HSAN
Vasculitis – present as mononeuritis multiplex	Younger age at onset; pain is the hallmark of vasculitic neuropathy; associated systemic features like purpura, skin rashes, lung or kidney involvement; proximal muscle weakness in severe illness; characteristic features on nerve biopsy point towards vasculitis
Diabetes – distal, axonal neuropathy	Presentation of diabetic neuropathy is similar to amyloidosis as there is a presence of distal, symmetrical axonal neuropathy associated with evidence of focal entrapment. But severe autonomic dysfunction, relentless progression, presence of systemic involvement favour amyloidosis
Toxic neuropathies	Arsenic toxicity can present as painful, sensory > motor, axonopathy. But the presence of CNS involvement, Mees' line, skin hyperkeratosis and the absence of autonomic disturbance favour toxic neuropathy. Disease stabilisation after stopping exposure to toxin

(Alkhawajah et al. 2014; Joint Task Force of the EFNS and the PNS 2010)

46.7 Management

Management of PPN is mainly based on immunosuppressive agents, symptomatic therapy for pain and dysautonomia associated with PPN and systemic complications. Immunosuppressive agents like corticosteroids, cyclophosphamide (CP) and rituximab have been tested in PPN and intravenous immunoglobulin (IVIg) and plasma exchange (PE) have been used for rapid benefits and sometimes for maintenance. Response to these agents depends on the subtype of PPN.

46.7.1 Immunosuppressive Agents

IgM-MGUS and DADS-M do not show favourable response to any of these immunosuppressive agents. In contrast, IgG or IgA-MGUS respond favourably to immunosuppression (steroids, IVIg and PE). High-dose cyclophosphamide with whole body irradiation or rituximab can be helpful to patients after failure of previous treatment. Treatment of POEMS is directed against underlying plasma cell tumour under the guidance of oncologists. For solitary osteosclerotic lesion, radiation and excision are useful. In patients with multiple osteosclerotic lesions, high-dose chemotherapy with stem cell transplantation results in good outcome. Lenalidomide, cyclophosphamide, melphalan and corticosteroids have been found to be useful in various regimens. In multiple myeloma, chemotherapeutic options like bortezomib, thalidomide and lenalidomide have been studied. Therapeutic regimens of these agents are beyond the scope of this book. But, it is important for clinicians to reiterate that some of these chemotherapeutic medications hold a potential to aggravate neuropathy. PE, CP, rituximab and steroids can be useful in Waldenstrom macroglobulinaemia when there is rapid progression of symptoms. In amyloidosis, stem cell transplantation can produce complete remission in more than 50% of patients. Alternatively, chemotherapeutic agents with steroids have been used with limited success. PE, rituximab and anti-HCV therapy help to mitigate neuropathy associated with cryoglobulinaemia.

46.7.2 Pain and Dysautonomia

Pain associated with SFN can be severe and should be treated with pregabalin, amitriptyline, gabapentin or duloxetine. Choice of these agents is based on tolerability and side-effect profile. Management of dysautonomia has been discussed in case study (Table 46.5).

Table 46.5 Management of autonomic dysfunction

Autonomic dysfunction	Nonpharmacological intervention and medical treatment
Orthostasis	**Nonpharmacological intervention:** Treatment is primarily nonpharmacological. Patients should be trained in activities that require the use of muscle pump action to improve circulation and mitigate fainting while standing, e.g. crossing of legs in a scissor pattern and slightly leaning forward while standing, crossing of legs in seated posture; squatting involves powerful pressor activity and can be used to abort hypotensive episodes; orthostatic standing training involves leaning patients upright with the upper back against a wall and the feet away from wall about 1 foot for 10–20 min once or twice a day; support garments over lower limbs can be helpful; dietary measures such as 6–10 gm salt and 2–3 L of water/day can be helpful; drinking 500 mL of water up on awakening or before meals helps to increase blood pressure by 30–40 mmHg for a duration of 1–1.5 h; avoid carbohydrate-rich foods as they significantly lower blood pressure **Medical treatment:** 1) fludrocortisone increases blood volume secondary to sodium retention. It is started in dose of 0.05 mg ½ tablet and increased up to 0.2 mg/day. Side effects are weight gain, supine hypertension, pulmonary oedema, hypokalaemia and pedal oedema 2) Midodrine: It is a sympathomimetic agent which has minimal or no central nervous system effects. Most patients require 2.5–10 mg every 3–4 hourly, up to a maximum of 60 mg per day. Owing to the risk of supine hypertension, it should be avoided after 6 pm. Transient goose flesh can occur with midodrine 3) Droxidopa: This precursor of norepinephrine has been recently approved for treatment of orthostatic hypotension 4) Pyridostigmine: It is an anticholinesterase inhibitor and increases neural transmission at nicotinic receptor in the autonomic ganglia. It is given at doses of 30 mg thrice daily and can be increased to 90 mg three times per day
Supine hypertension	The use of short-acting antihypertensives like captopril, propranolol or nifedipine is preferred to treat supine hypertension
Bladder dysfunction	Anticholinergics such as tolterodine and solifenacin are useful in patients with urinary urgency and frequency. In cases of voiding dysfunction, pro-cholinergics like bethanechol and pyridostigmine may help. If residual volume is persistently more than 100 mL, then clean self-catheterisation should be considered
Bowel dysfunction	Laxatives help to ameliorate constipation. Erythromycin and metoclopramide can be used to improve gastric motility

46.7.3 Systemic Complications

Apart from management of neurological features, attention should be given to systemic manifestation of these plasma cell disorders, when they exist. Comorbidities like anaemia, hyperviscosity syndromes, renal failure, hypercalcemia and diabetes mellitus should be dealt with appropriate therapy to improve the overall prognosis (Rison and Beydoun 2016; Ramchandren and Lewis 2012; Joint Task Force of the EFNS and the PNS 2010; Raheja et al. 2015).

46.8 Prognosis

Long-term follow-up of these patients is necessary, as there is possibility of malignant transformation in a proportion of patients with MGUS. Risk factors for malignant transformation are levels of M protein >3gm/dL, the presence of Bence Jones proteinuria, bone marrow plasmacytosis >10%, age > 70 years and raised ESR (Kwan 2007). Neuropathies associated with MGUS other than IgM appear to be more responsive to treatment. Neuropathy is known to respond favourably to therapy, when pathophysiology is primarily demyelinating as in IgG/IgA-MGUS and POEMS (Raheja et al. 2015). PPN associated with multiple myeloma, Waldenstrom macroglobulinaemia and amyloidosis are challenging to treat as they have predominantly axonal changes and develop systemic complications as well.

46.9 Case Study

Clinical details: A 64-year-old male patient presented with pain in both lower limbs, which began 4 months before presentation. Pain used to worsen with walking and exertion. He also noticed tingling and burning sensation in both feet and legs simultaneously. One month prior to presentation, he noticed change in speech and difficulty in manoeuvring food bolus in mouth. He also developed unintentional weight loss of 10 kg. There were no features suggestive of hypothyroidism. There was no history of upper limb involvement, giddiness, presyncope or bowel/bladder dysfunction. On examination, he had macroglossia (Fig. 46.1) and restriction of tongue movements on either side. The liver and spleen were not enlarged. There was no

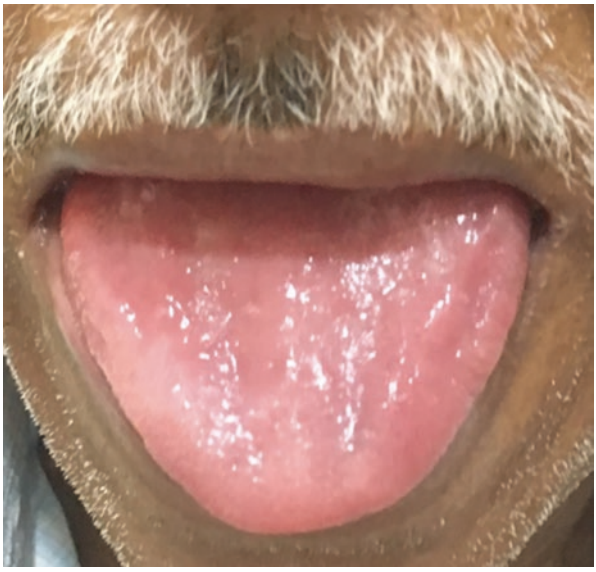

Fig. 46.1 Macroglossia in a patient with amyloidosis

lymphadenopathy. There was no palatal or facial weakness. Pinprick, temperature and vibration sensations were reduced in both feet in a graded manner up to middle part of leg. Both ankle reflexes were absent and knee reflexes were depressed. The patient had mild difficulty in walking on heels and toes. His muscles were firm to hard to touch, most prominently on the thighs. Nerve conduction studies showed severe, axonal, sensorimotor, distal + proximal polyneuropathy affecting lower limbs more than upper limbs. In addition, there was evidence of median nerve entrapment at the wrist. Needle electrode examination was normal. Creatine kinase (CK) levels were normal. ESR was 61, CBC was normal and sugar levels were within normal limits.

Summary: A 64-year-old male patient presented with sensorimotor axonal neuropathy, median nerve entrapment, macroglossia and weight loss.

Discussion: The combination of macroglossia, sensorimotor axonal neuropathy and nerve entrapment can occur with hypothyroidism, acromegaly and amyloidosis. Thyroid profile and growth hormone levels were within normal limits. SPEP revealed the presence of M band (Fig. 46.2). Quantitative immunoglobulin levels showed severe elevations in serum IgA and free kappa light chains, but lambda light chains were normal. Bone marrow biopsy showed plasmacytosis (15% plasma cells).

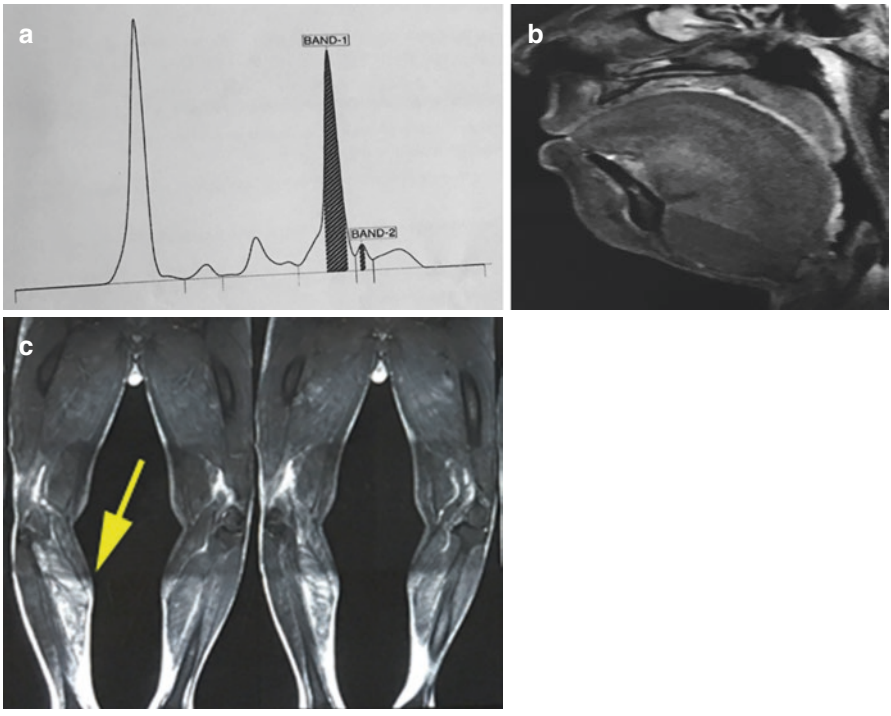

Fig. 46.2 (**a**) Prominent M band on SPEP, amyloid deposition in (**b**) tongue and (**c**) gastrocnemius muscle (*yellow arrow*) in a patient with amyloidosis (Courtesy: Department of Radiology, Bombay Hospital, Mumbai)

These investigations pointed towards amyloidosis. To evaluate tongue hypertrophy and myalgias, muscle MRI was done. It showed infiltration of tongue and calf muscles (Fig. 46.2). 2D Echo did not show any cardiac dysfunction.

Is this primary, secondary or familial amyloidosis?

Amyloidosis can be classified into three types (Table 46.6):

Table 46.6 Classification of amyloidosis

Type of amyloidosis	Salient features
Primary systemic (AL) amyloidosis	It occurs with clonal proliferation of plasma cells. Elevated lambda light chains on SPEP and quantitative immunoglobulin assay. Presents as sensorimotor, axonal neuropathy, autonomic dysfunction, macroglossia and organomegaly. Restrictive cardiomyopathy can occur
Secondary (AA) amyloidosis	It occurs secondary to chronic infections and inflammatory diseases. It is characterised by extracellular tissue deposition of fibrils that are composed of fragments of serum amyloid A (SAA) protein, a major acute-phase reactant protein produced predominantly by hepatocytes. Proteinuria, weight loss and pedal oedema are most common manifestations
Familial amyloid polyneuropathy (FAP)	Transthyretin (TTR) FAP has presentation similar to primary systemic (AL) amyloidosis except that elevated light chain assay and bone marrow biopsy are normal

Final diagnosis: primary systemic amyloidosis (AL) with amyloidotic neuropathy

Key Points

When to suspect

- Axonal, small fibre or CIDP, DADS-M type of neuropathy
- Prominent autonomic neuropathies
- Median neuropathy in males
- Unexplained weight loss

How to diagnose

- Immunofixation electrophoresis
- Electrodiagnosis of neuropathy pattern

How to treat

- Treatment of the haematological condition
- Immunotherapy

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Miller Fisher Syndrome

47

47.1 Introduction

Miller Fisher described three patients having 'an unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia)'. These patients were similar to the midbrain form proposed by Guillain (Fisher 1956). Bickerstaff's description of patients with ophthalmoplegia, ataxia and hypersomnolence came around the same time. These patients had additional central involvements (Bickerstaff 1957). When all the three features (ataxia, areflexia and ophthalmoparesis) are present, the constellation is designated as classical MFS. MFS subtypes can have incomplete features on one end and more extensive features at the other. Though phenotypically different, GBS and MFS subtypes share a number of clinical features including the presence of antecedent infection, a monophasic evolution, areflexia and albuminocytological dissociation in the cerebrospinal fluid. Some patients of MFS, during the course of illness, may show overlapping features with GBS, like extensive weakness.

47.2 Clinical Features

47.2.1 Classical MFS

Classical MFS patients have ataxia, areflexia and ophthalmoplegia.

47.2.2 Incomplete Form of MFS

47.2.2.1 Acute Ophthalmoparesis

These patients have ophthalmoparesis as the main or only clinical finding. The ophthalmoparesis may be complete, affecting all movements or could be partial, e.g. sixth nerve palsy. Ptosis and dilatation of pupil may be seen, in addition to the eye

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movement restrictions or, rarely, by themselves. When they occur in isolation, the presence of anti-GQ1b antibodies may lead to the diagnosis and in fact, these cases might represent a very incomplete form of MFS.

47.2.2.2 Ataxic GBS

Patients in this group present with severe incoordination. They do not have eye movement abnormalities, and deep tendon reflexes may be depressed. Anti-GQ1b IgG antibodies, when present, support the diagnosis of this incomplete form of MFS. The incoordination is thought to be caused by selective dysfunction of muscle spindle afferent mediated by anti-GQ1b antibodies.

47.2.2.3 Acute Sensory Ataxic Neuropathy

Patients present with severe sensory ataxia without ophthalmoplegia. Romberg's test is positive in them. Anti-GQ1b antibodies with or without anti-GD1b IgG antibodies are seen in a proportion of patients.

47.2.3 Bickerstaff Brainstem Encephalitis (BBE)

BBE patients exhibit hypersomnolence, ophthalmoplegia and ataxia. Some patients have hyperreflexia, another feature of the central involvement. In a proportion of patients, ophthalmoplegia may be absent. The presence of anti-GQ1b or anti-GD1b antibodies can be resorted to, to confirm the clinical diagnosis of these MFS subtypes.

47.2.4 MFS and GBS Overlap

Patients with MFS or BBE who develop limb weakness overlap with GBS. Almost half of the patients who begin as MFS later develop overlaps with GBS or BBE. Such overlap is usually seen in the first week of the onset of Fisher syndrome (Sekiguchi et al. 2016).

47.3 Pathophysiology

GQ1b is strongly expressed in the third, fourth and sixth cranial nerves and on the muscle spindles. Hence, anti-GQ1 antibodies can be conceptualised to result in ophthalmoplegia and ataxia. It is believed that GQ 1 is expressed in the reticular formation as well which may explain the somnolence seen in patients with BBE. Like GBS, molecular mimicry in relation to the infective agent is the basis of MFS. The neuromuscular junction is also known to be affected in few patients (Lo 2007).

47.4 Investigations

47.4.1 Anti-GQ1b Antibody

Present in two thirds of patients with BBE and 80–90% of patients with MFS. These antibodies form an important tool in the workup of restricted forms.

47.4.2 Magnetic Resonance Imaging (MRI) and Electrophysiological Studies

In patients having BBE phenotype, MRI can show abnormalities in a small proportion. MRI is only occasionally abnormal in the MFS phenotype. EEG record may be abnormal in both BBE and MFS. On electrophysiology, sensory nerve action potentials tend to be of low amplitude, H reflexes are absent and F waves can show abnormalities. These changes are known to exist in minority of patients with BBE.

47.5 Differential Diagnosis

Condition	Key differentiating features
Brainstem stroke	Long tract signs, lower cranial nerve palsies
Myasthenia gravis	Fatigable ptosis, chewing and swallowing difficulty, rest helps
Botulism	Clinical setting, ptosis
Wernicke's encephalopathy	Clinical setting, memory changes, benefit with supplementations
Brainstem encephalitis	Convulsions, long tract signs, CSF cellularity, MRI changes

47.6 Management

MFS is a self-limiting condition. Both plasmapheresis and intravenous immunoglobulins have been used in the therapy of MFS. Such immunotherapy is particularly relevant when the patient shows features of BBE and CNS involvements GBS (Overell and Willison 2005).

47.7 Prognosis

MFS cases are generally benign, do not recur and have a favourable prognosis (Heckmann and Dütsch 2012).

Key Points

When to suspect

- Ataxia, ophthalmoplegia and areflexia in varying proportions

How to diagnose

- Diagnosis of exclusion
- Electrophysiology: reduced SNAPs and absent H reflexes
- Anti-GQ 1b antibody

How to treat

- IVIg or PE

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