Acquired Neuromuscular Disorders

Pathogenesis, Diagnosis and Treatment

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Foreword

This book, by Corrado Angelini and collaborators, represents a comprehensive resource which covers one perhaps often underestimated area, acquired neuromuscular disorders, within the field of clinical myology. Compared to the more known group of genetic diseases, acquired neuromuscular disorders represent a wide heterogeneous group of diseases, in terms of etiology, clinical manifestations, and treatment, nonetheless of growing interest regarding the pathogenic mechanisms, relationships with more systemic disorders, as well as the possibilities to intervene with targeted therapies. Social, individual health system delivery and environment modifications occurred in the last years plenty justifies the continuous increasing interest in improving knowledge on them.

Chapters addressing important issues in etiopathogenesis include diseases caused by autoimmune, as well as toxic, endocrine, nutritional, and infectious factors. Also a chapter on amyotrophic lateral sclerosis is included, as a model for neurodegeneration. Finally, specific chapters are devoted to the most recent investigative tools diagnosis of neuromuscular disorders is nowadays based upon.

In doing so, the authors have collected plenty of accessible information of practical use for clinicians and trainees dealing with muscle disease.

Neuromuscular clinical research is a complex field of study starting from biochemistry or molecular pathology to complex disease physiopathology. In doing this effort to cover recent practical management of a patient with such a disorder, the editor in chief, a well-known expert in the field, is accompanied by highly qualified colleagues, a lot of them working within the scientific area of myology in Italy or also abroad but in tight collaboration with Italian neuromuscular centers, one more reason why I am very proud, as current President of the Italian Association of Myology (AMI), to present this work being confident that the interested audience will appreciate its reading.

Pisa, Italy
2016

Gabriele Siciliano
President of the Italian
Association of Myology (AIM)

Preface

Acquired diseases of the muscle, nerve and neuromuscular junction have for many years been neglected by the pathologist and were not presented in a book dedicated for the clinician.

The past few years, however, have seen a renewed and growing interest by the application of new techniques in diagnosis, such as the use of specific autoantibodies, new antibodies discovered in myasthenia gravis and peripheral neuropathies, that have lead to the recognition of a series of new disorders, such as necrotizing myopathy, MuSK myasthenia or several types of dys-immune neuropathies.

MRI has seen a considerable advancement both in nerve and muscle pathology with a diagnostic impact and has also provided new basis for the interpretation of muscle pathology.

This book covers both diagnostic and therapeutic features by the collaboration of many authors who have developed the field. A book of this kind requires close collaboration between several authors who I thank for their contribution and for timely sending their chapters.

I also acknowledge Andrea Ridolfi and Springer for their help and support, in collecting the contributions, which as ever is much appreciated.

Venice, Italy
2016

Corrado Angelini

Contents

Introduction

Although the first recorded case of polymyositis was described by Wagner as long ago as 1863, the acquired inflammatory muscle conditions have received comparatively little attention until recently. The frequency of inflammatory myopathies is still debated.

A peripheral neuropathy may be defined as a disease causing motor, sensory or autonomic dysfunction of the peripheral nervous system. There are certain frequently acquired neuropathies such as leprosy, certainly the major cause of acquired peripheral nerve disease in the developing countries today, in both lepromatous and tuberculoid forms. Diabetes mellitus and vitamin deficiencies cause frequent diseases of peripheral nerves. Finally, the current ageing of the population brings a mixed bag of myalgias, many ills of muscle weakness and cramps and loss of function of motor and sensory nerve. Acquired neuromuscular disorders represent therefore an increasing cause of disability in the population.

Acquired myopathies and neuropathies result from several different diseases, including endocrine, inflammatory, paraneoplastic, drug- and toxin-induced disorders, critical illness myopathy, and metabolic myopathies. Most of the inflammatory myopathies can have a chance of association with malignant lesions. Paraneoplastic neuropathies are also a new field that has several important developments and constitutes a difficult entity to be diagnosed and treated.

Neuropathies of dys-immune origin can be treated by immunosuppressants, IVIg or monoclonal antibodies.

Several advances in the management and treatment were reached in the last two decades but need a critical reappraisal by experts in the field.

The purpose of this book is to review the advances that diagnostic autoantibodies and MRI have brought to the field of acquired neuromuscular disorders and to provide to the clinician and the pathologist a comprehensive guide to the application and interpretation of these techniques in everyday practice, presenting new therapies.

Part I

Diagnostic Tools

Autoantibodies in Neuromuscular Disorders

1

Luis Querol, Eduard Gallardo, and Isabel Illa Sendra

1.1 Antibodies in Autoimmune Neuromuscular Disorders

1.1.1 General Principles

The search for autoantibodies is an important topic of research in autoimmune diseases. Describing highly disease-specific antibodies is usually the first step leading to the description of the pathogenic mechanisms involved in the development of an autoimmune disease. The field of neuromuscular diseases was the first one describing a disease-specific, relevant, pathogenic autoantibody, when antibodies against the nicotinic acetylcholine receptor (AChR) were described four decades ago [1]. Since then, many other autoantibodies, in the myasthenia field, inflammatory neuropathies and myositis, have been described.

The description of specific autoantibodies has a three-fold utility. First, they inform about the target antigen and are the first step to describe the upstream and downstream mechanisms leading to loss of tolerance or to tissue damage in an autoimmune disease. On the other hand, autoantibodies, when they are specific enough, have diagnostic implications and may uncover disease subtypes with different pathogeneses, prognoses, or responses to treatment. The discovery of anti-MusK antibodies in myasthenia [2], for example, led to the description of a disease subtype in which clinical features and response to conventional therapies significantly differ from those of typical myasthenia with antibodies against the acetylcholine receptor [3]. Finally, specific autoantibodies are frequently used to monitor the response to treatment. This is not useful for all antibody-mediated diseases, but in some, the correlation is clear.

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The quest for specific autoantibodies in neuromuscular disorders has not been easy, and, still today, some diseases in which the involvement of humoral factors was suspected since their description do not have identifiable autoantigens that could serve, at the same time, for the study of their pathogenesis and as diagnostic biomarkers [4]. There are several clinical, technical, and interpretation caveats when studying the importance of autoantibodies in neuromuscular diseases. From the clinical perspective, neuromuscular disorders are often diagnosed with clinical, electrophysiological, or pathological criteria that don't necessarily reflect common pathogenic mechanisms. This, in fact, leads to high degree of clinical heterogeneity within the classical syndromes. Defining clinically homogeneous subgroups, no matter how infrequent they are, is the necessary step to avoid noise when searching for specific antigenic reactivities. The technical problems that have frequently misguided autoantibody search are, first, the use of biased approaches (candidate-antigen approach, animal models, etc.); second, the bias toward the identification of protein antigens (and negligence, with the exception of inflammatory neuropathies of glycolipid, lipid, and glycidic antigens); and third, the use of techniques that detect non-conformational antigens, such as Western blot. Western-blot-detected autoantibodies can have some clinical utility but not always recognize true pathogenic antigens. Finally, when an autoantibody is detected, interpretation of the findings is not always easy. Researchers tend to look for sensitive antibodies that are present in a high proportion of patients of the studied syndrome, when the description of very specific antibodies (regardless of their frequency) might be more relevant. These are common problems to other antibody-mediated autoimmune diseases that now try to be overcome using multimodal autoantibody search approaches.

High disease specificity, homogeneous clinical features associated to it, relevance of the antigen in disease pathogenesis, membrane location, and existence of knockout animal models of the antigen resembling the autoimmune disease phenotype are the features that strongly suggest the importance of the antigen found.

1.2 Autoantibodies to Neuromuscular Junction Components

Autoimmune disorders of the neuromuscular junction (NMJ) include myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS). In these pathologies, a series of autoantibodies to different pre-or postsynaptic NMJ antigens have been identified and some of them have been proven to unequivocally contribute to their pathogenesis. In clinical practice, to test for the autoantibodies to NMJ proteins is useful for their precise diagnosis and prognosis and in some cases to select a specific treatment.

1.2.1 Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disease characterized by muscle weakness, fatigability, and autoantibodies against proteins of the skeletal muscle

membrane at the NMJ. MG is a "classical antibody-mediated autoimmune disease" caused, in most cases, by autoantibodies directed against the acetylcholine receptor (anti-AChR antibodies). Significant progress was made in the knowledge of MG immunopathology when the pathogenic role of the anti-AChR antibodies was demonstrated long ago [5, 6].

The search for novel antigenic reactivities in seronegative myasthenia (SNMG) patients has been a hot topic in MG research that, recently, has led to the description of autoantibodies to the muscle-specific kinase (MuSK) in up to 50 % of patients without autoantibodies to AChR [2, 7], autoantibodies to lipoprotein-related protein 4 (LRP4), or autoantibodies to "low-affinity" acetylcholine receptor (AChR) antibodies [8–10]. Finally, we found that a group of seronegative MG have autoantibodies to cortactin [11]. According to these findings, the percentage of seronegative MG has been dramatically reduced.

A number of autoantibodies to proteins of the skeletal muscle – anti-striated muscle antibodies – such as titin, myosin, actin, and anti-ryanodine receptor antibodies may be present in MG patients [12].

Therefore, MG is not only a clinically but an immunologically heterogeneous disease, as determined by its various subgroups, AChR+, MusK+, LRP4+, low-affinity AChR+, cortactin, and seronegative MG [13].

1.2.1.1 Autoantibodies to Acetylcholine Receptor

The acetylcholine receptor autoantibody response is T cell mediated. The pivotal role of the acetylcholine receptor autoantibodies in the pathogenesis of MG was demonstrated long ago. The anti-AChR antibodies were shown to act basically through three main mechanisms, including a) the destruction of the postsynaptic membrane by complement pathway activation, leading to a reduced expression of AChR at the muscle endplate, b) the blockade of the acetylcholine binding to the receptor by antibodies attached to the acetylcholine binding site, or c) reduction of the number of functional AChRs by increasing their degradation and turnover due to the cross-linkage of AChRs by divalent antibodies [14, 15]. Further demonstration of its pathogenic role came from the demonstration that the removal of the antibodies by plasma exchange produced important clinical benefits to the patients [16].

1.2.1.2 Autoantibodies to MuSK

In MuSK MG, the autoantibodies are against the receptor tyrosine kinase MuSK at the neuromuscular junction. A characteristic of these antibodies is that they are of the IgG4 isotype. IgG4 is a peculiar antibody isotype, formed by divalent heavy-light-chain pairs [17]. Several studies demonstrate the pathogenic properties of MusK antibodies [18–22]. It has been shown that IgG4 MuSK antibodies prevent MuSK to interact with LRP4 in a complement-independent manner [21]. The lack of MuSK- Lrp4 interaction would interfere with the AChR clustering pathway explaining why MuSK antibodies produce myasthenia. In MusK, unlike AChR+– MG, there is a clear correlation between severity and antibody levels [23, 24]. None of the Musk-MG patients have thymoma.

1.2.1.3 Autoantibodies to LRP4

Antibodies against LRP4 were described in a subgroup of SNMG patients [9] and, in additional studies, it was confirmed that a subset of seronegative MG have autoantibodies to this NMJ protein [8, 25, 26]. Prevalence ranges from 12 to 50 % of AChR- and MusK-double-negative patients, probably due to ethnic and/or technical differences in the published studies. A recent study indicates that the incidence of this antibody is likely to be very low [27]. The role of these antibodies in causing myasthenic symptoms in vivo has not been completely elucidated [28]. It is proposed that they can inhibit the interaction of agrin-LRP4-MuSK and disrupt AChR aggregation. No specific MG phenotype has been associated to antiLRP4 antibodies although it was described that these patients have a more severe clinical phenotype [9]. Furthermore, the prevalence of antiLRP4 antibodies in seropositive MG cohorts and in other autoimmune diseases is still to be clarified as well, to determine their specificity.

1.2.1.4 Low-Affinity Antibodies to AChR

It was reported that up to 66 % of patients with SNMG have low-affinity IgG1 antibodies against the AChR that are only detectable in a cellular assay using HEK cells co-transfected with human AChR subunits and rapsyn to induce AChR clustering on the cell surface [10]. Later on, the same authors reported that up to 50 % of patients with SNMG, generalized or ocular, have antibodies that recognize clustered AChR and their levels correlate with the electrophysiological features. These antibodies fix complement and decrease miniature motor endplate potentials to the same extent as antiAChR antibodies, suggesting a pathogenic role comparable to that of classical antiAChR antibodies [29]. Low-affinity anti-AChR-antibody test is not currently commercially available. Patients with this type of autoantibodies generally have an ocular MG or a mild generalized disease.

1.2.1.5 Autoantibodies to Cortactin

We reported the presence of autoantibodies to cortactin, a NMJ subsarcolemmal membrane protein, in 20 % of SNMG patients [11]. Testing for these antibodies, in addition to clinical and electrophysiological studies, can be used as a potential marker of an underlying immune mechanism related to a suspected MG. Cortactin is needed for the formation of AChR clusters. Cortactin signaling downstream from agrin/MuSK promotes actin polymerization and AChR/rapsyn clustering [30]. These functions of cortactin indicated that it could be a new antigen playing a role in the development of MG. However, the fact that cortactin autoantibodies are found not only in SNMG but also in some patients with AChR+ antibodies could indicate that their role is the pathogenesis of the disease is secondary to the disease process, maybe as a consequence of epitope spreading or structural damage of the NMJ.

1.2.1.6 Striational Antibodies

Some patients with MG have autoantibodies to proteins expressed in the cytoplasm of the striated muscle. These striational antibodies do not participate in the pathogenesis of the disease but they may have some value as predictors of disease severity

or thymoma [31]. For instance, they are detected in 75–85 % of patients with MG and thymoma, particularly in young patients. The presence of titin and RyR antibodies in early-onset MG (<50 years) has a 90 % positive predictive value and a 95 % predictive negative value for thymoma. However, these antibodies are not so clearly associated to disease severity [32].

1.2.2 Lambert-Eaton Myasthenic Syndrome (LEMS)

LEMS is a rare autoimmune disease of the neuromuscular junction in which predominant symptoms are lower limb weakness and dysautonomia, due to acetylcholine release failure in the presynaptic terminal. Almost 60 % of patients present as a paraneoplastic syndrome, in which small-cell lung carcinoma is the most frequent associated tumor. Ninety percent of LEMS patients have antibodies against voltage-gated calcium channels (VGCC) of the P/Q type. Although it has not been formally demonstrated, these antibodies are thought to have pathogenic potential. They target a membrane channel that is relevant in disease pathogenesis, disease can be transmitted from mother to child during pregnancy, mutations in the VGCC result in a LEMS-like phenotype, and active immunization in rats determines a mild LEMS-like disease in the animals.

An important issue in LEMS care is ruling out a hidden neoplasm. Anti-SOX1 antibodies are present in a high proportion of small-cell lung carcinoma-associated LEMS patients while are absent in non-paraneoplastic LEMS. These antibodies are, thus, a very good biomarker with immediate clinical implications in the search for a hidden neoplasm in LEMS [33].

1.2.3 Autoantibody Testing

1.2.3.1 Diagnosis

The study of autoantibodies to the NMJ proteins should be done, for diagnostic purposes, in all patients with suspected MG. Antibodies against AChR are found in around 85 % of patients with MG, while anti-MusK antibodies are detected in 5–10 % of patients previously classified as seronegative [13]. The finding of these autoantibodies confirms unequivocally the diagnosis of MG and distinguishes subgroups of autoimmune MG. Although patients may have very similar clinical characteristics, it is now established that MG-MuSK+ patients are predominantly young females and have a preferential involvement of facial, bulbar, and axial muscles. Furthermore, the diagnosis of MG-MuSK+ may have therapeutic implications. We reported the clinical, immunologic, and long-term response to rituximab of patients with MuSK + MG and AChR + MG resistant to other therapies. A benefit of the therapy was observed in both groups of patients; however, in view of the long-lasting benefit observed in MuSK + MG patients, we recommend to use rituximab as an early therapeutic option in this group of patients with MG if they do not respond to prednisone [3].

The study of LRP4 in selected SNMG patients will help to define the clinical characteristics of this subgroup of MG and the presence of cortactin Abs in patients with suspected SNMG may help to support the diagnosis of immune MG and consequently the use of immune therapy.

1.2.3.2 Correlation with Disease Severity

Studies addressing the diagnostic value and the correlation of antiAChR antibody titers and disease severity were done long ago [16, 34] and are reviewed periodically [35]. It is well known that anti-AChR-antibody titers vary among patients. In general, patients with ocular MG have lower titers than patients with generalized MG. However, patients with similar degrees of weakness may have quite dissimilar titers of anti-AChR antibodies and, consequently, cannot reliably predict the severity of disease in individual patients. Even though a clear relationship between intra-individual AChR-antibody titer variation and changes in the clinical status has not been fully shown, the antiAChR antibody test is widely used by clinicians, in individual MG patients, to evaluate clinical status and especially used as prognostic markers regarding response to treatment. A retrospective study showed that antibodies against the main immunogenic region of AChR differentiate between ocular and generalized MG [36]. A recent study found a weak correlation between change in AChR-antibody concentration and clinical status. The study showed that concentration of AChR antibodies fell in most patients regardless if they improved or not. Also, they considered that the antibody follow-up might be useful as a marker for non-response or inadequate immunotherapy [37]. Another recent study examined the association between concentration of AChR antibodies and MG clinical status in individual patients over time. Their results indicated that, for MG patients with immunosuppressive treatment, repeated antibody measurements had a predictive value for therapeutic decisions [31].

Autoantibodies to MuSK correlate with disease severity [23, 24] and have been demonstrated useful as markers of response to immune therapy. For instance, rituximab has shown effectiveness in both AChR+ and MusK MG. However, while AChR-antibody titers varied along the follow-up and did not correlate with disease improvement, MuSK antibodies decreased dramatically during the follow-up after a single rituximab cycle, the response was long lasting, and it was associated with a dramatic clinical improvement [3]. No studies are available for LRP4, low-affinity AChR, or cortactin antibodies.

1.3 Antibodies in Inflammatory Neuropathies

The field of inflammatory neuropathies is one of the fields in which the discovery of autoantibodies has yielded more relevant results, especially in Guillain-Barre syndrome (GBS) and its variants [38–40]. More recently, the discovery of autoantibodies directed against structures of the node of Ranvier has placed the focus on chronic inflammatory demyelinating polyneuropathy (CIDP) variants harboring these antibodies and has boosted research on the topic [41–43].

1.3.1 General Considerations

The inflammatory neuropathies are a heterogeneous group of peripheral nerve disorders that can be acute (GBS and its variants) or chronic (CIDP, multifocal motor neuropathy, polyneuropathy associated to monoclonal gammopathy of unknown significance, etc.) that share an immune-mediated pathogenesis [44]. The search of autoantibodies has been the main topic of immunopathological research in all the diseases of this group since the description of the first animal models of experimental autoimmune neuritis [45]. The autoantibodies described in these diseases share several common features that are not frequent in other autoimmune diseases. First, the antigens described are usually glycosylated structures, mainly glycosphingolipids (gangliosides) and glycoproteins [38, 46, 47]; second, the detection of specific autoantigens has led to the discovery of specific microbial strains associated to the development of the disease [48]; and, third, the discovery of autoantibodies has helped defining small subgroups of patients with homogeneous clinical features.

1.3.2 Guillain-Barre Syndrome and Variants

1.3.2.1 Antiganglioside Antibodies

GBS is the most frequent inflammatory neuropathy. In GBS it is widely accepted that the peripheral sensitization to a microbial antigen results in an immune response that includes antibodies against microbial structures [49]. These antibodies, by a molecular mimicry mechanism, cross-react with nerve molecules that share some structural similarities with microbial antigens and fix complement, determining nerve pathology. The development of the axonal motor variant of GBS after a *Campylobacter jejuni* infection is the first and best characterized model of molecular mimicry in a human autoimmune disease [48]. In this model, a patient with a *C. jejuni* gastrointestinal infection develops antibodies of the IgG subclass against the lipooligosaccharides (LOS) of the *C. jejuni* bacterial wall. The structural similarity of the LOS with the nerve ganglioside GM1 determines a cross-reaction of the antibodies directed against the bacterial structures with nerve structures and, finally, complement fixation leading to nerve damage [50–52]. Although a less frequent variant, this same model, explains the axonal sensory and motor variant of GBS, in which IgG anti-GM1 antibodies are also present, in vitro and in vivo studies support this disease model that reinforces the importance of molecular mimicry in the development of acute post-infectious autoimmune diseases.

Miller-Fisher syndrome (MFS) is an uncommon variant of GBS in which, again, the peripheral sensitization to a microbial antigen precedes the development of ophthalmoparesis, ataxia, and areflexia [53, 54]. In this case the microorganisms involved and the mechanisms leading to a cross-reactivity are not characterized in detail. However, up to 95 % of patients develop antibodies against the GQ1b ganglioside with very high specificity. The GQ1b ganglioside is abundant in the muscle spindles, oculomotor nerves, and nerve roots, and, thus, the presence of

complement-fixing autoantibodies directed against these structures ultimately leads to the development of the typical features of the disease. Passive transfer studies in animal models demonstrate the pathogenic potential of the anti-GQ1b autoantibodies in MFS [55]. Not surprisingly, anti-GQ1b antibodies have a diagnostic accuracy for MFS that exceeds that of lumbar puncture and represent one of the best examples of the clinical utility of defining homogeneous clinical subgroups to detect highly specific and clinically relevant autoantibodies. The detection of anti-GQ1b autoantibodies can also help detecting patients that do not present with the typical clinical features, such as those few including brainstem signs like Bickerstaff's encephalitis variants of the MFS or those with *forme fruste* variants such as ataxic GBS or pure isolated ophthalmoparesis, in which anti-GQ1b antibodies are also positive [54].

Antiganglioside antibodies are also useful in the clinical definition of other GBS variants. For example, anti-GT1a antibodies are frequently found in the rare pharyngeal-cervico-brachial palsy variant of GBS and antibodies directed against gangliosides bearing disialosyl epitopes (GD1b, GD3, GT1a, GQ1b) can be detected in a significant proportion of patients with acute ataxic neuropathy [56].

1.3.2.2 Other Autoantibodies in GBS

Despite the description of antiganglioside reactivities has led to a better understanding of the disease pathogenesis and to clinical utility in some GBS variants, in the acute inflammatory demyelinating polyradiculoneuropathy (AIDP) variant, the most frequent one in the western world, the discovery of specific autoantibodies remains elusive. Disease onset and progression of the AIDP variant share many features with the other GBS variants and the response to intravenous immunoglobulin and plasma exchange supports a role of humoral factors in its pathogenesis. Several studies describe antibodies against gangliosides, myelin and axonal proteins, node of Ranvier structures, and intracellular antigens. So far, none of these autoantibody reactivities has been replicated or demonstrated useful for clinical practice. A recent study detected antibodies against moesin [57], an intracellular Schwann cell protein expressed at the nodes of Ranvier in patients in which AIDP arises after a cytomegalovirus infection. Although it is interesting that the autoantigen can differ depending on the trigger of the disease, this report includes a limited number of patients and needs independent confirmation. Some reports describe antibodies against other node of Ranvier structures in some GBS patients. Several groups described antibodies against neurofascin-155, neurofascin-186, NrCAM, contactin-1, or gliomedin in AIDP [41, 43]. These results however are yet to be confirmed.

1.3.3 Chronic Inflammatory Neuropathies

The group of chronic neuropathies with immune-mediated pathogenesis mainly includes CIDP, multifocal motor neuropathy (MMN), and polyneuropathies associated with monoclonal gammopathy of unknown significance (MGUSP). Despite

their clinical heterogeneity, these diseases share their response to immune therapies and, as in acute inflammatory neuropathies, the study of autoantibodies has been the main topic of research in their immune pathogenesis.

1.3.4 Chronic Inflammatory Demyelinating Polyradiculoneuropathy

CIDP is the most frequent disease of the group. Experimental evidence and the response to intravenous immunoglobulin and plasma exchange suggest an immune-mediated pathogenesis and a role for humoral factors in its pathogenesis [58, 59]. As it happens with the AIDP variant of GBS, clinically useful antibodies have been elusive despite extensive research efforts. This is particularly true for the typical variant of CIDP, in which there is no autoantibody serving as a useful biomarker in the everyday practice.

1.3.4.1 Antibodies Against Node of Ranvier Structures

The field of autoantibodies in CIDP has recently regained interest after the description of small subsets of patients harboring antibodies against node of Ranvier structures with clinical utility [41–43]. Our group and others described the presence of a subset of CIDP patients that reacted against neurons and node of Ranvier structures. A subset of patients reacted against contactin-1 (CNTN1), an axonal protein of the paranode of Ranvier that forms a dimer with contactin-associated protein-1 (CASPR1), essential for maintaining nodal integrity and saltatory conduction. We described that patients harboring anti-CNTN1 antibodies present with a typical clinical pattern that includes aggressive onset, motor predominance, axonal damage at onset, and poor response to intravenous immunoglobulin [42]. Recent reports by independent groups confirm the association of anti-CNTN1 antibodies to this specific subset of CIDP and reinforce the idea that these antibodies have diagnostic and prognostic potential for a subset of CIDP patients [60].

Neurofascin 155 (NF155) is the glial ligand of the CNTN1–CASPR1 complex and is also essential for the maintenance of the paranodal loops at the axo-glial junction that enable node of Ranvier integrity and salutatory conduction. A German group detected antibodies against NF155 in a few patients with CIDP and GBS [43] and a Japanese group reported an increased frequency of these autoantibodies in patients with combined central and peripheral nervous system demyelination [61]. Our group described that patients harboring anti-NF155 antibodies present with typical features that include distal predominance, a prominent intention tremor, and lack of response to intravenous immunoglobulins [62]. These results await confirmation in independent cohorts.

Interestingly both anti-CNTN1 and anti-NF155 antibodies are of the IgG4 isotype [46, 62]. IgG4 is an anti-inflammatory autoantibody that is unable to activate complement or bind Fc gamma receptors in inflammatory cells. This means that the autoantibody itself has to be pathogenic interfering with the function of the target antigens. A report by the group of Dr Faivre-Sarrailh describes that anti-CNTN1

antibodies disrupt the union between CNTN1/CASPR1 and NF155 and determine paranodal disruption in in vitro models [46]. However, formal demonstration of the pathogenicity of these autoantibodies is still pending. The studies on CNTN1 and NF155 in CIDP and the development of different techniques (cell-based assays, immunoprecipitation) have boosted the interest in describing new antigenic reactivities in immune neuropathies and questioned the homogeneity of CIDP as a single entity [39].

1.3.4.2 Antibodies Against Myelin Proteins

Considering the demyelinating nature of CIDP, most initial studies, using the candidate-antigen approach, focused in the description of antibodies against myelin proteins in CIDP. Some studies found antibodies against myelin protein zero, myelin protein 2, connexin 32, or myelin protein 22 [63]. These autoantibodies were found in significant proportions in control populations or in hereditary neuropathies and CIDP specificity was not confirmed in other cohorts.

1.3.4.3 Antiganglioside Antibodies

A few reports also link CIDP to antibodies against glycosphingolipids. LM1 ganglioside is the predominant ganglioside in peripheral myelin. Some reports describe antibodies against the LM1 ganglioside in a small subset of CIDP patients that presented more frequently with ataxia than anti-LM1 negative CIDP patients [64].

1.3.5 Multifocal Motor Neuropathy

Multifocal motor neuropathy (MMN) is a chronic, focal, exclusively motor neuropathy that responds to intravenous immunoglobulin. As most diseases of the group, it is diagnosed based in clinical and electrophysiological criteria that, in this case, include the presence of nerve conduction blocks. The immune pathogenesis of the disease, again, is inferred from the fact that it responds to intravenous immunoglobulin [65].

Approximately half of the patients with MMN have IgM antibodies against the GM1 ganglioside. These autoantibodies bind to node of Ranvier structures of motor axons (where GM1 is enriched) and fix complement, disrupting nodal and paranodal molecular organization. These autoantibodies cause motor dysfunction in an analogous way IgG anti-GM1 antibodies do in axonal GBS. Nevertheless, anti-GM1 testing leaves half MMN without identifiable antigens. Some authors propose that testing antibodies against combinations of gangliosides could increase the frequency of patients positive and, thus, improve the diagnostic yield of these autoantibodies. For example, testing IgM antibodies against the galactocerebroside/GM1 complex increased the sensitivity of the test to 75 % (from a 48 % when testing anti-GM1 antibodies only) [66]. Some series also describe IgM antibodies against GM2 gangliosides in a subset of MMN patients but their frequency is much lower than GM1.

Recent reports propose the presence of antibodies against neurofascin-186 and gliomedin in up to 60 % of patients with MMN (with and without anti-GM1 antibodies). These results however await independent confirmation [67].

1.3.6 Polyneuropathy Associated to Monoclonal Gammopathy of Unknown Significance (MGUS-P)

Monoclonal gammopathy frequently associates with immune neuropathies. In CIDP, for example, up to 10 % of patients can present with an IgG or IgA gammopathy of unknown significance. Whether this association is key in the disease pathogenesis is unknown. Up to 50 % of patients with an IgM monoclonal gammopathy have a polyneuropathy, regardless of the origin of the gammopathy (Waldenstrom's macroglobulinemia, multiple myeloma, MGUS, etc.) [68]. Approximately 50 % of these patients have a specific demyelinating neuropathy characterized by distal phenotype, large-fiber sensory predominance, distal tremor, slow progression, and poor response to conventional immune therapies that associates to antibodies against myelin-associated glycoprotein (MAG) [47]. Anti-MAG antibodies define a specific subgroup within all IgM monoclonal gammopathy-associated polyneuropathies with diagnostic and prognostic implications. Deposition of IgM and complement fixation in myelinated fibers of these patients and the development of a demyelinating neuropathy when animals are immunized with MAG suggest that, although studies are scarce, the anti-MAG antibodies can be pathogenic [69].

A very infrequent chronic, demyelinating, ataxic neuropathy associated with ophthalmoparesis and IgM monoclonal gammopathy (CANOMAD) presents with antibodies against disialosyl epitope-bearing gangliosides (such as GD1b, GQ1b, GD2, GD3) of the IgM isotype, defining, again, a specific disease subtype with diagnostic and therapeutic implications within the group of neuropathies associated to IgM monoclonal gammopathy [70].

1.3.7 Other Diseases of the Peripheral Nerve

1.3.7.1 Neuromyotonia

Although very infrequent, autoimmune neuromyotonia is another disease in which recent discovery of disease-specific associated autoantibodies has changed its diagnosis and knowledge on its pathogenesis. Contactin-associated protein 2 (CASPR2) is a protein of the juxtaparanode that is necessary for potassium channel function and normal saltatory nerve conduction. One of the antigens targeted by antibodies initially attributed to voltage-gated potassium channel complex antibodies in Morvan's syndrome and peripheral nerve disorders with peripheral nerve hyperexcitability was identified as CASPR2 [71]. Studies on the pathogenicity and clinical features associated to these autoantibodies are still pending.

1.4 Myositis-Specific Autoantibodies

1.4.1 General Considerations

A number of antibodies against skeletal muscle antigens have been described in inflammatory myopathies [72, 73]. These antigens are mainly intracellular; therefore its pathological significance is still under debate. In this section we will describe briefly each autoantibody discovered so far in the different inflammatory myopathies that can be used for the diagnosis/prognosis of these diseases. Table 1.1 summarizes the most relevant autoantibodies in myositis.

Table 1.1 Myositis-specific autoantibodies

Antibody	Target antigen	Frequency	Diagnosis	Useful clinical features
Anti-Jo1	Histidyl-t-RNA synthetase	15–20 %	PM, DM, IMNM, ASS	Mechanic hands ILD, heart involvement
Anti-PL7	Threonyl-t-RNA synthetase	5 %	PM, DM, IMNM, ASS	Mechanic hands ILD
Other anti-synthetases	Otras t-RNA synthetases	<5 %	PM, DM, IMNM,ASS	Mechanic hands ILD
Anti-TIFIγ	Transcriptional intermediary factor γ	6 %	DM adult	Cancer
Anti-Mi2	Nucleosome remodeling deacetylase	6 %	DM	–
Anti-MDA5	Melanoma differentiation-associated gene 5	6 %	DM Amyopathic	ILD
Anti-SAE	Small ubiquitin-like modifier-activating enzyme	<5 %	DM adult	Dysphagia
Anti-SRP	Signal recognition particle	5 %	IMNM	Heart involvement
Anti-NXP2	Nuclear matrix protein 2	<5 %	DM adult > DM juvenile	Cancer
Anti-HMGCR	3-Hydroxy-3-methyl glutaryl coenzyme A reductase	6 %	IMNM	–
Anti-cN1A	Cytosolic 5' nucleotidase 1A	30 %	IBM	Dysphagia, distal weakness UULL

Modified from Allenbach [72]
Abbreviations: *ILD* interstitial lung disease, *PM* polymyositis, *DM* dermatomyositis, *IBM* inclusion body myositis, *IMNM* immune-mediated necrotizing myopathy, *ASS* anti-synthetase syndrome, *UULL* upper limbs

1.4.1.1 Anti-synthetase Antibodies

Multiple antibodies to different aminoacyl t-RNA synthetases have been described. These are enzymes expressed in the cytoplasm that bind the amino acids that have affinity for each transference RNA (t-RNA). Anti-Jo-1 (anti-histidyl-t-RNA synthetase) are the most frequently found associated to myositis and can be found in 25–30 % of patients with dermatomyositis (DM) and polymyositis (PM). The prevalence of the other anti-synthetase antibodies falls down to 1–5 % and includes anti-threonyl-t-RNA synthetase (PL7), anti-alanine-t-RNA synthetase (PL12), and anti-glycyl-t-RNA synthetase (EJ) among others. After Jo-1, anti-PL7 and anti-PL12 are the most frequently detected and are associated with a less severe myositis but a more severe interstitial lung disease (ILD) than Jo-1.

Patients with reactivities against these antigens share a wide variety of clinical features such as ILD, arthritis, fever, and skin lesions known as "mechanic hands." All these different manifestations are known as anti-synthetase syndrome, although not all patients with these antibodies show all these clinical features. Some patients with acute or subacute myalgias and weakness associated to anti-synthetase antibodies can present necrotizing myopathy features in the muscle biopsy.

1.4.1.2 Anti-Mi2 Antibodies

Anti-Mi2 targets the Mi2/NuRD complex that participates in chromatin remodeling. This complex participates in development and differentiation of T and B cells and the formation of the basal lamina of the epidermis. They are found almost exclusively in patients with DM (10–30 %). They have been related to skin changes, better response to corticosteroids, and a lower risk of developing cancer.

1.4.1.3 Anti-TIF-1γ Antibodies

Initially called anti-p155/140, transcriptional intermediary factor γ (TIF-1γ) antibodies are detected in patients with DM, especially in those associated to neoplasia. Therefore, this biomarker is relevant to the early detection of one of the major complications that represent a serious risk for the patient. 50 to 100 % of patients, depending on the series, with DM and neoplasia have these antibodies in Japan. In contrast, in Europe and America between 15 and 20 % of patients with DM without neoplasia are also positive for these antibodies. This discrepancy could be explained not only by racial differences but also different criteria to select patients. The sensitivity and specificity together with the negative and positive predictive values obtained by ELISA and Western blot are similar to those obtained using radiolabeling-based immunoprecipitation; therefore this last technique could be substituted by the former ones [74].

1.4.1.4 Anti-SRP Antibodies

Signal recognition particle (SRP) is a ubiquitously expressed protein involved in the transport of newly synthesized proteins to the endoplasmic reticulum. Although formerly associated to classical myositis, it is now accepted that they are associated to necrotizing myopathies that can also present with lung, heart, or skin involvement.

1.4.1.5 Anti-HMGCoAR Antibodies

The enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) is a key molecule in the biosynthesis of cholesterol. The presence of antibodies against HMGCR is associated with patients treated with statins who develop a myopathy some time after initiating the treatment. However, these antibodies have been also found in patients that have not taken statins. Typically these antibodies have been found in patients with clinical features of a necrotizing myopathy. However, in lower percentages they have been also found in patients with DM, PM, and IBM.

1.4.1.6 Anti-MDA5 Antibodies

Melanoma differentiation-associated gene 5 (MDA5) is a RNA helicase that belongs to the family of intracellular receptors of innate immunity as a defense against viral infections. Sato et al. discovered in 2005 the presence of these antibodies in Japanese population. Anti-MDA5 antibodies have been found exclusively in patients with amyopathic dermatomyositis, and most of them develop a rapidly progressive interstitial lung disease that often has fatal consequences. Therefore, detection of these antibodies is of high prognostic value for these patients.

1.4.1.7 Anti-SAE Antibodies

Anti-small ubiquitin-like modifier-activating enzyme (SAE) identifies a subgroup of patients with adult DM. Most of them present skin lesions and systemic features that can include dysphagia. These antibodies have been associated to the haplotype HLA DRB1*04-DQA1*03-DQB1*03 [75].

1.4.1.8 Anti-NXP2 Antibodies

The target antigen of these antibodies is the nuclear matrix protein 2. These antibodies are very infrequent, are associated to cancer, and have a higher incidence in adult DM.

1.4.1.9 Anti-cN1A Antibodies

The presence of antibodies against different nuclear and cytoplasmic antigens in skeletal muscle in patients with IBM had been reported years ago, especially in those patients with a monoclonal gammopathy [76]. Recently, using mass spectrometry analysis, it has been reported that antibodies to a 44KDa protein that had been called Mup44 recognize the cytosolic 5' nucleosidase 1A. These antibodies are detected at high titers in 30 % of patients with IBM and only in 4 % of patients with DM or PM and therefore constitute the first serological marker of this disease [77, 78].

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Electromyography

2

Lucio Santoro and Fiore Manganelli

2.1 Introduction

Myopathies are a heterogeneous group of diseases induced by numerous pathogenic mechanisms that include many different phenotypes and show a variable muscle pathology. Diagnostic approach can be simple in some instances, but it can also be ambiguous when symptoms are very light or when the hyposthenia involves distal muscles. In the majority of cases, a careful clinical examination, the personal and family history, and the biochemical data are sufficient to formulate a differential diagnosis with a neurogenic process. When this is not possible, the most useful investigations are the electrodiagnostic studies and more specifically the muscle examination by means of needle EMG. This technique is also very useful for guiding the choice of the muscle to be eventually biopsied, to characterize the distribution of the involved muscles, and to set the severity of the myopathy. Nerve conduction studies and tests for neuromuscular transmission (NMT), which includes the repetitive nerve stimulation (RNS) and single-fiber electromyography (SFEMG), are needed in special cases with the aims to confirm the clinical suspect of a NMT disorder and to establish whether it is presynaptic or postsynaptic.

In this chapter, we will illustrate the neurophysiologic findings most useful for the differential diagnosis of a myopathy with respect to a neurogenic disease, and moreover we will try to correlate EMG findings with muscle pathology with the aim to give useful data for the identification of a specific form of myopathy.

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2.2 Anatomo-physiological Basis

A motor neuron in the anterior horn of the spinal cord, its axon, and all the muscle fibers it innervates constitute a motor unit (MU), according to the definition of Sherrington [1]. The MU is the smallest part of a muscle that can be activated voluntarily. The number of muscle fibers belonging to the same MU (innervation ratio) varies considerably among the muscles. Normally, the muscles which perform fine movements have few fibers for MU (i.e., 5–10 in the external muscles of the eye), while muscles whose task is to generate as much strength as possible can have thousand of fibers in their MU (i.e., almost 2 thousand in the gastrocnemius muscle). Each MU occupies a circular territory in the muscle of about 5–10 mm in diameter, and in this area, fibers of several MU (from 5 to 30) are intermingled. The distribution of muscle fibers in the cross-sectional area of a muscle shows that fibers sharing the same innervation (belonging to the same MU) are generally isolated, less often in pairs and very rarely they are associated in number of three or more. This peculiar distribution avoids the interference between twitches of neighboring MUs and limits the interaction between action potentials of muscle fibers of the same MU. According to their biochemical and physiological characteristics, the MUs of human muscle can be classified into three main groups, namely, the slow-twitch, oxidative type which have the smallest axons, slow firing frequency, high content of oxidative enzymes, low content of glycogen and phosphorylase, and high resistance to fatigue and express low tension. The second type of MUs is called fast-twitch, oxidative, and glycolytic type, and they have high content of both oxidative enzymes and glycogen and phosphorylase; they also have high resistance to fatigue but can express a medium tension. The last type are the fast-twitch, glycolytic type; these MUs have the largest axons, high content of glycogen and phosphorylase, low content of oxidative enzymes, and low resistance to fatigue but can express a high tension during bursts of high-frequency discharge [2]. The electrical activity produced by voluntary contraction of muscles or in response to motor nerve stimulation can be recorded by intramuscular electrodes (needle EMG) or by cutaneous electrodes (motor nerve conduction) and is a very important tool for the investigation of muscle and peripheral nerve diseases. Cutaneous electrodes can record the electrical potential generated by the whole muscle (compound muscle action potential, CMAP), while concentric needle intramuscular electrode can record the electrical potential generated by a single MU (motor unit potential, MUP); both potentials are in volume since they are recorded in the extracellular space; therefore, their peak-to-peak voltage declines steeply with radial distance from muscle fibers that originate the corresponding transmembrane potential. Needle electrode can also capture the single-fiber potential when they originate spontaneously from a denervated muscle fiber and are called fibrillation or denervation potentials. The MUPs recorded with a concentric needle electrode have three parameters that need to be considered for a reliable evaluation of the investigated muscles: duration, amplitude, and morphology. All the parameters largely depend on the number of muscle fibers, belonging to the same MU, included in the recording area of the electrode, on their caliber, and on their degree of synchronization. In other words, the clustering of muscle

fibers of the same MU close to the leading-off surface of the electrode will increase the peak-to-peak amplitude of the MUP; vice versa, a reduced number of muscle fibers will reduce the amplitude. However, if the caliber of few surviving fibers is clearly increased (i.e., hypertrophic fibers), it is still possible to record a high-amplitude MUP. The MUP duration is a more stable and repetitive parameter than the amplitude and largely depends on the number of the MU fibers present in a large recording area (almost 2.5 mm). Therefore, the pathological processes which induce primary loss of muscle fibers habitually also determine a reduced MUP duration, while the diseases which imply axon sprouting or regeneration with clustering of muscle fibers belonging to the same MU increase MUP duration. The MUP morphology can vary from the classical biphasic or triphasic shape to a polyphasic shape (more than four phases crossing the baseline) when muscle fibers do not discharge synchronously. This can happen when the neuromuscular transmission is compromised or when noncontractile tissues (lipids or connective) have modified the MU spatial distribution. All the MUP parameters vary according to the patient age and the examined muscle; therefore, every evaluation must be performed with respect to the normative data that should be produced by the laboratory which has performed the neurophysiological exam. The CMAP amplitude is the most important parameter for evaluating the integrity of MU number in an examined muscle. However, some variability due to technical and anatomical aspects is always present, and a variation from normal values of at least 40 % should be considered. In addition, it is true that the loss of motor units is the most frequent cause of reduction of CMAP amplitude; however, if there is a severe loss of muscle fibers in a long-standing dystrophic process, the same finding can also be recorded. The order of MU recruitment is task related and can also vary according to the preexisting experience. However, the size principle of Henneman is the rule when a gentle movement is required; therefore, the small MU will be recruited first [3]. Thereafter, if a greater tension is needed, the large MU will intervene. The electromyography system can analyze the single MUPs of small MU, but cannot see individual MUP of large MU, which can be analyzed only by automatic system. It is possible to record the MU recruitment, and this is normally progressively increasing until a maximum where the single MUP cannot be recognized from each other (interference pattern). This technique needs the cooperation of the patient and is anyway difficult in some muscles (e.g., gastrocnemius). With this limitations, it is however possible to observe a reduced recruitment pattern (single oscillations or mixed pattern) with high amplitude in neurogenic diseases, while a fast interference pattern with low amplitude is frequent in myopathic diseases, at least if this is not very long lasting. Overall, a normal MUP requires that in the recording area of the needle electrode, muscle fibers of a single MU are present with normal density and have a homogenous caliber and an efficient neuromuscular transmission. When a disease modifies the anatomical setting with a new pattern that occupies a large part of the muscle, the MUP parameters will change accordingly. In these cases, the analytical evaluation of at least 20 MUPs will show an increase or a decrease of duration and of amplitude and a high or normal percentage of polyphasic shape. All myopathic processes change the anatomical picture of the muscle, and many induce a prevalent

pattern. However, some muscular diseases are characterized by a variegated anatomical picture in the muscle, and the EMG findings will change and will depend on the characteristic of the area where the needle has been collocated. Therefore, one of the most striking EMG findings in muscle diseases is the high variability of MUP parameters in the same muscle.

The neuromuscular junction (NMJ) consists of the motor axon terminal, the synaptic cleft, and the highly organized postjunctional folds on the muscle membrane. The chemical transmitter at the NM junction is acetylcholine (ACh). The nerve terminal is the site of synthesis and storage of ACh, which is released in the discrete quanta. The quanta are located in three separate stores: primary (immediately available), secondary (mobilization store), and tertiary (reserve store). The number of ACh molecules in each quantum was estimated to be fewer than 10,000.

When a nerve action potential depolarizes the presynaptic terminal, voltage-dependent calcium channels are activated, allowing an influx of calcium that results in a release of ACh from the presynaptic terminal through the proteins of SNARE complex. A nerve impulse results in a release of 50–100 quanta.

The ACh diffuses across the synaptic cleft and binds to ACh receptors (AChR) on the postsynaptic membrane, resulting in an end-plate potential (EPP).

In the healthy condition, the EPP always reaches the threshold for the opening of voltage-gated sodium channel on muscle membrane, and hence EPP triggers a muscle fiber action potential (MAP) that, propagating along sarcolemma down T tubules, results in muscle contraction. The amplitude of the EPP above the threshold value needed to generate a MAP is called the safety factor (SF).

The SF is reduced in patients with a disorder of NMT. The failure of the EPP to reach MAP threshold represents the basis of the electrodiagnostic abnormalities in patients with disorders of NMT [4]. The resulting impulse blocking accounts for the decremental responses seen on repetitive nerve stimulation (RNS) studies and the impulse blocking seen with single-fiber electromyography (SFEMG). In addition, the time variability of when the EPP reaches MAP threshold accounts for the neuromuscular jitter seen in the latter technique [5, 6].

SFEMG is an electromyography (EMG) technique that allows to record action potentials from individual muscle fibers (i.e., single MAPs). The selectivity of this technique relies on the small recording surface of needle electrodes. This can be obtained by using either dedicated SFEMG needle electrodes that have a small recording area (0.0005 mm^2) or conventional EMG needle electrodes after proper filter setting since these have larger recording area (0.07 mm^2).

SFEMG recordings can be performed during electrical stimulation of the nerve (S-SFEMG) or during voluntary activation (V-SFEMG) of the tested muscle [7–10].

When MAPs are elicited by nerve stimulation, the latency from stimulus to response (i.e., MAP) varies. This variation is due to physiologic fluctuation in the time for EPP to trigger MAP, and it represents the neuromuscular jitter.

When SFEMG is performed during voluntary activation, the needle electrode, inserted into the tested muscle, records from two or more MAPs that belong to the same motor unit (MU) and that hence depolarize synchronously. In this case, the

neuromuscular jitter is the variations in the time intervals between pairs of MAPs. This variation is related to physiologic fluctuation in the time that EPP takes to trigger each MAP in the examined pair of potentials.

Jitter is the most sensitive electrophysiological measure for the safety factor of NMT. In disorders of NMJ, the reduction of EPP may cause a delay in triggering MAPs, or if the EPP falls below the threshold, MAP is not generated. In the former, jitter will be increased; in the latter, SFEMG recording will demonstrate neuromuscular blocking. For *V-SFEMG* the subject is asked to maintain a steady contraction, and recordings of two or more MAPs belonging to the same MU can be performed by dedicated SFEMG or conventional EMG needle electrode. Around 20 different potential pairs are collected from the tested muscle. Theoretically, all muscles can be investigated with SFEMG. However, OO and EDC muscles are commonly investigated in clinical practice even though in some patients (e.g., MuSK positive), the examination of the most severely involved muscles to demonstrate abnormal jitter may be necessary. The following parameters should be recorded: the mean jitter (MCD) of all ($n=20$) potential pairs or stimulated MAPs, the percentage of potential pairs or stimulated MAPs in which jitter is abnormal, and the percentage of NM blocking.

The SFEMG examination is considered abnormal if at least one of the following criteria is satisfied:

1. The mean jitter (MCD) of all potential pairs or stimulated MAPs recorded exceeds the upper limit of mean jitter for that muscle.
2. Ten percent or more of potential pairs or stimulated MAPs have jitter that exceeds the upper limit of normality in that muscle or if more than 10 % of potential pairs/stimulated MAPs exhibits NM blocking.
   (a) Generally, NM blocking is observed when also jitter value is markedly increased.

Repetitive nerve stimulation (RNS) is a variant of the nerve conduction study since electrical stimulation is delivered to a motor nerve repeatedly several times per second [6].

The function of NMT is assessed by measuring after a train of stimuli the change in amplitude/area of the compound muscle action potential (CMAP) that represents the sum of the individual MAPs generated in a muscle. The train of stimuli may be carried out at low- (3 Hz) or high-frequency stimulation (20–50 Hz).

Low-frequency stimulation (e.g., train of 10 stimuli at 3 Hz) causes a depletion of ACh level in synaptic space since after the releasing of primary (immediately available) storage, it will be needing a time of 1–2 s for the mobilization of quanta from secondary storage. In this meantime, the amplitude of the EPP reduces (this phenomenon is known as synaptic fatigue). However, in normal subjects for the safety factor, EPP never falls below the threshold needed to generate a MAP. Vice versa for patients with NMJ disorders, the EPP of some muscle fibers may fall below the threshold level, and MAPs will not be generated. This reduction of MAPs is responsible for decremental response of CMAP when performing RNS studies.

The size of CMAP may be assessed by measuring either the amplitude or the area of the negative peak of the CMAP. In disorders of NMT, there is a progressive decrement of the second through the fourth or fifth response, with some return toward the initial size during the subsequent responses, a so-called U-shaped pattern. Decrement is defined as the percent change comparing the negative peak amplitude or area between the fifth (or fourth or lowest potential) and the first CMAP. The decrement is generally considered abnormal when greater than 10 %.

High-frequency stimulation (20–50 Hz for 5–10 s) may be used to investigate presynaptic level of NMJ. The high-frequency stimulation induces (rate faster than time needed [100–200 ms] for exit of calcium from terminal nerve) the accumulation of calcium ions in the preterminal space producing a transient increase in the amount of ACh released from the motor nerve. This greater ACh release increases the EPP and may improve synaptic transmission briefly (this phenomenon is known as facilitation). In healthy subjects, the EPP is already (safety factor) above the threshold for eliciting MAP, and high-frequency stimulation does not induce any change in CMAP size. A phenomenon of "pseudofacilitation" (increase of amplitude associated with reduction of duration of CMAP; area remains unmodified) can be observed, and it is attributed to increased synchronization of MAPs or to hyperpolarization of the muscle fiber membrane from increased sodium-potassium pumping. In normal muscle, pseudofacilitation may increase the CMAP amplitude to 50 % during stimulation at rates up to 50 Hz.

In a patient with a disorder that affects NMJ at presynaptic level (e.g., Lambert-Eaton myasthenic syndrome), after single electrical stimulus, few quanta of ACh are released, and the EPP frequently fall under the threshold. Therefore, the CMAP size may be reduced after single electrical stimulus, while during (or immediately after) high-frequency stimulation, the calcium accumulation in terminal nerve causes a massive releasing of ACh, and the EPP raises above MAP threshold resulting in an incremental response of CMAP. An increment greater of 60–100 % is considered of significance.

High-frequency stimulation is painful and requires patient tolerance, and thus in clinical practice, maximal voluntary muscular contraction (protracted for 10–60 s) is used to obtain the same effect of high-frequency nerve stimulation.

After the phase of facilitation, NMJ develops a phase of postactivation exhaustion, in which less ACh is released by each nerve impulse. The exhaustion lasts 2–5 min (maximum at 3 min) after the end of activation. In this period, low-frequency stimulation worsens the decrement of CMAP or may unmask a decrement not evident at the basal stimulation performed before the activation. Generally, after 5 min the change of CMAP size observed during low-frequency stimulation comes back to basal condition. RNS is more likely to be abnormal in proximal and facial muscles, rather than in limb distal muscles. To have the maximum diagnostic sensitivity, examination of several muscles, including those that are involved clinically, may be necessary. Hand muscles are easy to test but scarcely sensitive. Recording can be made from thenar or hypothenar muscles by stimulating median or ulnar nerves at wrist. Such stimulation is suitable if prolonged high-frequency stimulation is required. Proximal muscles have greater sensitivity than distal muscles. The

trapezius is the easiest shoulder muscle to test. The spinal accessory nerve is stimulated at the neck where it is superficial so that it can be maximally stimulated with low-intensity pulses, minimizing discomfort and stimulation of other muscles. Recordings can be also made from biceps brachii or deltoid muscles by stimulating musculocutaneous nerve in the axilla or axillary nerve at the Erb point. However, such stimulations are often disturbed by movement artifacts and stimulation/activation of near muscles. Facial muscles have the greatest sensitivity. Recordings are made from orbicularis oculi or nasalis muscles by stimulating facial nerve at tragus or stylomastoid foramen. This study may be performed with the patient either sitting or lying. Temperature influences the CMAP size and decremental response is less evident when the muscle is cool. Low temperatures reduce enzymatic activity of acetylcholinesterase in synaptic cleft, increasing the availability of ACh and increasing the EPP. Hand or foot muscles should be warmed to a surface temperature of at least 34 °C to avoid false negative results in patients with a disorder of NMT. In a patient with suspected disorder of NMT, the standard procedure consists of:

1. Low-frequency stimulation (10 stimuli at 3 Hz) to detect the decrement of CMAP amplitude/area.
2. If the test is positive (decrement of CMAP >10 %), the patient should undergo:
   (a) High-frequency stimulation (20 Hz for 5 s) or preferentially maximal voluntary muscular contraction (protracted for 30 s) to evaluate facilitation
   (b) Low-frequency stimulation every minute up to 5 min to evaluate postactivation exhaustion
3. If the test is negative (decrement of CMAP ≤10 %), the patient should undergo:
   (a) High-frequency stimulation (20–50 Hz for 5–10 s) or preferentially maximal voluntary muscular contraction (protracted for 60 s)
   (b) Low-frequency stimulation every minute up to 5 min in order to unmask a decremental response of CMAP during the phase of postactivation exhaustion

The high-frequency stimulation or maximal voluntary muscular contraction is essential in detecting presynaptic neuromuscular diseases by showing a significant increment of CMAP size (>60 %). If a small CMAP amplitude is observed at basal examination after single electrical stimulus, a presynaptic disorder should be strongly suspected. In this case, also a brief maximal voluntary muscular contraction (10 s) may be sufficient to disclose an incremental response of CMAP size.

In the next paragraphs, we will describe how to plan the EDX examination and the interpretation of most frequent findings according to the anatomical picture [11, 12].

2.3 Plan of the Electrodiagnostic Examination

Nerve conduction studies (NCS) in patients with suspected myopathy should include at least one motor and one sensory recording, in at least one upper and lower limb. Both sensory and motor nerve conduction studies are generally

normal in myopathies. However, in some distal phenotypes, it is possible that the loss of muscle fibers is enough to decrease the CMAP amplitude, but in this case, the distal latency and motor conduction velocity should be normal. Needle EMG is required to differentiate a motor neuron disease. A reduced CMAP amplitude is also present in case of presynaptic disorder (e.g., Lambert-Eaton disease), and a differential diagnosis is required by means of RNS. Sensory nerve conduction could be distally reduced in some myopathic disorders as the myotonic dystrophy type 1 or the critical illness myopathy, in which sensory endings can be involved in the context of a coexistent neuropathy. Proximal and distal muscles should be investigated, and upper and lower limb of one side must be considered. The most easy muscle to explore are deltoid, biceps, abductor digiti minimi, quadriceps (rectus), and tibialis anterior; however, the choice should be guided by clinical observation or by the diagnostic hypothesis. If an inclusion body myositis (IBM) is supposed, the flexor digitorum muscle should be considered; when a glycogen storage disease (e.g., Pompe disease) is a possibility, then paraspinal muscles must be investigated. In this case, cervical and lumbosacral levels should be avoided for the frequent coexistent radiculopathy, and a thoracic level is the best choice. EMG analyses can help for choosing the muscle to be biopsied; it should be a weak but not severely affected muscle. The EMG examination is more sensitive than clinical observation and can reveal an involved muscle that has escaped clinical evaluation. However, the biopsy cannot be performed in a muscle recently investigated by needle EMG. Needle EMG should give data about the presence of muscle irritability on insertion of the needle, the state of the muscle at rest, and the analyses of MUPs during slight effort. Finally, it is important to record the recruitment behavior at moderate and maximum effort [13].

2.4 General Findings

2.4.1 Resting Activity

In a normal resting muscle, the only electrical activity that is possible to record derives by the miniature end-plate potentials when the needle electrode is very close to the end plates. However, the needle introduction in the muscle can induce discharges of MFs that are called insertional activity and is generally very short (less than 250 ms). This activity is produced by the mechanical irritation of the needle electrode on the nearby end plate. The insertional activity can be abnormally prolonged when the muscle is denervated or in case of myotonias, polymyositis, or some muscular dystrophies suggesting an aspecific hyperexcitability of MFs. However, the normal insertional activity can also be decreased, e.g., in long-lasting or end-stage myopathies, when most of the muscle fibers are replaced by fat or connective tissue. In this case, it is also possible to feel an increased resistance to needle insertion due to the advanced fibrotic substitution of the muscle. Other types of abnormal electrical activity can

originate in the muscle itself [14] as fibrillations, complex repetitive discharges (CRD), and myotonia.

Fibrillation potentials are muscle fiber action potentials recorded outside the end-plate zone; are spontaneous, biphasic, or triphasic in shape; and are of very short duration (1–5 ms) [15]. They are generally seen in neurogenic diseases but can be present in several primary muscle disorders, as Duchenne muscular dystrophy, dermatomyositis and polymyositis, Pompe disease, sporadic inclusion body myositis (sIBM), and centronuclear myopathy (CNM). The origin of fibrillation potentials in these diseases can be produced by the denervation of muscle fibers secondary to focal fiber necrosis, as in Duchenne dystrophy, or to the inability of a regenerated but isolated fiber to be innervated for the excessive distance from the innervation zone. An additional explanation could be a modification of muscle membrane properties with an increased excitability. In polymyositis, it is also possible that there is an inflammatory direct damage of intramuscular axon branches [16]. Less consistently fibrillation can be observed in facioscapulohumeral (FSHD), limb girdle (LGMD), and oculopharyngeal dystrophies. Overall fibrillation potentials are the most frequently pathological spontaneous activity that can be observed in muscle diseases [17].

CRD are complex potentials showing multiple spike components, with a total duration ranging from 50 to 100 ms. They discharge repetitively at a low (5 Hz) or high (100) frequency, generally with a stable waveform that is typically polyphasic, from one discharge to another, and they have an abrupt onset and cessation. However, the waveform can change suddenly at the higher firing frequency due to the intermittent block of some spike components. The origin of CRD is the spontaneous firing of a pacemaker muscle fiber which ephaptically drives few or several adjoining muscle fibers [18]. The CRD have been described both in muscle and peripheral nerve diseases. Since CRD are very frequent in adult onset form of Pompe disease and especially in paraspinal muscles, they have been included as a diagnostic feature in the diagnostic guidelines of the American Association of Neuromuscular and Electrodiagnostic Medicine [19]. CRD are rarely observed in LGMD and FSHD, while they seem to be more frequent in Duchenne than in Becker muscular dystrophies [20]. CRD are also present in almost half of patients affected by sIBM, with a higher frequency in paravertebral muscles. According to a recent analysis, CRD seem to occur more frequently in myopathies with protein accumulations, vacuoles, and nuclear protein defects, e.g., Pompe disease, sIBM, and centronuclear myopathy, rather than in myopathies with a sarcolemmal protein defect, e.g., Becker and LGMD [17].

Myotonic rhythmic discharges can be induced by a voluntary movement or by an electrical or mechanical stimulation of a muscle and can be seen in congenital myotonias (induced by both Na and Cl channel alterations), dystrophic myotonia (DM1 and DM2), congenital paramyotonia, Pompe disease, and sodium channel myotonias. Myotonic discharges may be present with or without clinical myotonia. They are characterized by a burst of potentials, with positive or negative spikes, of short duration (less than 5 ms), which progressively increase and then decrease their amplitude and frequency of firing. The pathophysiology of myotonic discharges is

not completely known in human diseases, but it probably relates on Na and Cl channel abnormalities. In fact, a reduced conductance for chloride can reduce the leak of this ion in the transverse tubular extracellular space after the depolarization with a consequent relative increase of extracellular potassium concentration (K ions are released with chloride ions). This K concentration could raise until a level which determines depolarization of transverse tubular membrane with repetitive responses to a single presynaptic impulse. The reduced chloride conductance theory can be applied to congenital myotonia, but it has not been shown in myotonic dystrophies or congenital paramyotonia. In these diseases, mutations of Na channels can cause cellular membrane instability and sensibility to temperature. In fact, myotonic discharges are increased with cooling in DM1 and paramyotonia and with warming in DM2. Several observations describe a longer myotonic discharge in myotonic dystrophies than in congenital myotonias. The electrophysiologic differential diagnosis among myotonias can be approached using the short-exercise protocol. With this technique, the variation of amplitude of the CMAPs, habitually recorded in the abductor digiti minimi muscle, at baseline and after 10 s of maximum effort every 2 s for one minute can show three different patterns. These patterns have a good sensitivity and specificity in distinguishing among the chloride and sodium myotonias [21].

2.4.2 MUP Analysis

In myopathic disorders, the number of functional muscle fibers per MU is reduced. This has the consequence of a contraction of the area of the MUs, since some of the most distant fibers are lost. The MUP duration is largely dependent on the number of muscle fibers active in the relatively large (2.5 mm) recording area of the needle electrode; therefore, if the fiber loss is consistent, the MUP duration can be shortened. Sometimes the duration and the shape of the MUP suggest that it is composed by one fiber only. In this case, it is likely that the surviving fibers belonging to the same MU are too thin to evoke a recordable potential or too isolated by the recording electrode for the presence of no contractile tissue. This finding can be more evident in weak muscles and in patients with chronic myopathy [22, 23]. However, in some instances, the short and often polyphasic main component of MU potentials is linked to late or less often preceding small potentials that discharge several ms (at least 5 ms) far from the main component of the MUP. These satellite components, if included in the measure of the MUP duration, make it very long, sometimes more than 30 ms. This finding is recordable in dystrophic diseases when there is some fiber regeneration from satellite muscle fibers or from splitted fibers. Overall, MUP duration in myopathies is shorter than normal when MUPs with satellite components are not considered. The presence of MUPs with late component is frequent also in neurogenic diseases, but in this case short MUPs are not or exceptionally recorded. The amplitude of the main component of the MUPs depends on the number and diameter of muscle fibers very close (within 1 mm) to the recording area of the

needle electrode. This makes the amplitude parameter variable also in normal subjects when single MUPs are analyzed. In muscle diseases, the fiber loss and their reduced diameter induce habitually a reduction of MUP amplitude, but the occasional presence of hypertrophic fibers close to the electrode can determine an increased amplitude of a MUP spike, otherwise short in duration. Therefore, a highly increased variability of MUP amplitude can be a finding suggestive of a primary muscle disease.

The biphasic or triphasic shape of the majority of normal MUPs is due to the homogeneity of fiber diameter and to the regular distribution of end-plate zone within the MU area, with consequent synchronous contraction of the recordable component of the MU. When there is an increased variability of muscle fiber diameter, the reinnervation of splitted or regenerated fibers and the presence of fat or connective tissue, the synchrony of MU components can be lost, and MUPs can appear polyphasic and sometimes with late components. This finding is very frequent in many muscle disorders.

2.4.3 MU Recruitment

In normal subjects, the number and the discharge frequency of MUs recruited are proportional to the tension required by the voluntary movement. If the MUs have a reduced number of functional muscle fibers or there is uncoupling between electrical and mechanical events, it is necessary to increase the number and the rate of discharge of recruited MUs. This is what happens in myopathic patients when they are requested to develop a certain muscle tension. In other words, in muscle disorders, it is possible to see in weak muscles a recruitment pattern very similar to that of normal muscles (interference pattern) with regard to the richness of MUs, but with a reduced amplitude. The increased number of recruited MUs, their high rate of discharge, and the complex shape of MUPs all determine the interference patterns seen in myopathic patients even in weak contraction, while the reduced number of functional muscle fibers in each MU is the explanation of the reduced amplitude of the potentials. This finding can be no more present when the myopathic process is long lasting and has induced a severe reduction of muscle fibers with the possibility that the electrical activity of some MUs is no more recordable.

2.5 Specific Findings

Electromyographic findings obtained with needle electrode do not permit a differential diagnosis among the several muscle diseases. However, some peculiar aspects can orientate toward a specific myopathy and can likely anticipate the histological aspects. In the following paragraphs, these findings will be shortly described for some muscular dystrophies; inflammatory, endocrine, metabolic, and congenital myopathies; and myotonias.

2.5.1 Muscular Dystrophies

The most frequent muscular dystrophies are the dystrophinopathies, Duchenne muscular dystrophy (DMD), and Becker muscular dystrophy (BMD). The diagnostic procedure, after the clinical evaluation, can be addressed with genetic testing, particularly when there is a positive family history or in some cases on muscle biopsy. Therefore, the EMG examination may be helpful in sporadic cases when clinical and biochemical data are equivocal. In these cases, needle EMG can reveal increased insertional activity, some sparse fibrillation potentials, and short, small, polyphasic MUPs with early recruitment. In late stages, EMG findings can be somewhat different according to the supervening morphological changes (muscle tissue necrosis, muscle fiber splitting, reinnervation, and muscle replacement by connective and fatty tissue). In these stages, the insertional activity is reduced and alongside with short MUP; long duration MUPs with satellite components can be appreciated [23]. At the MU recruitment, the interference pattern may be incomplete.

In other dystrophies, as LGMD, FSHD, and oculopharyngeal needle EMG can be necessary when disease onset is in adult age, CK levels are mildly elevated and clinical data are not clearly expressed. In these forms of dystrophies, fibrillation potentials and CRD are rare, while MUPs can be short, small, and polyphasic [17]. The EMG can be also useful to evaluate the distribution of weak muscles.

2.5.2 Inflammatory Myopathies

In classical poly-dermatomyositis (PM and DM), the majority of patients show classical myopathic EMG abnormalities with short, small, and polyphasic MUPs, but the presence of spontaneous activity in the form of fibrillation potentials is a constant finding. In addition, the fiber irritability is revealed also by the occasional presence of CRD or myotonic discharges (only electrical). Fibrillation and CRD can decrease with the improvement of the disease [24]. On the other end, in long-lasting forms, it is possible that long duration and complex MUPs will appear, making the differential diagnosis with a neurogenic lesion more difficult. For this the MU recruitment and the distribution of involved muscles should be useful. In polymyositis, the EMG sampling of several muscles is also very useful for the choice of the muscle to be biopsied, since sometimes the biopsy can miss the morphological abnormalities.

The sporadic inclusion body myositis (sIBM) is likely a degenerative disorder rather than an inflammatory muscle disease; however, it is traditionally included in the inflammatory myopathy chapter. The electrodiagnostic findings are similar to those in DM and PM, but the incidence of the irritative aspects and the presence of a double population of MUPs, with myopathic and neurogenic aspects, is higher in IBM than in PM and DM [25, 26]. The differential diagnosis with a neurogenic disease can be further complicated by nerve conduction studies that can reveal a mild sensory axonal polyneuropathy in up to 30 % of patients with IBM [27]. A confirmatory muscle biopsy is mandatory.

2.5.3 Endocrine Myopathies

The presence of a thyrotoxicosis can be complicated by a concomitant autoimmune myasthenia gravis. This possibility must be excluded by adequate neurophysiological techniques. Otherwise, EMG analysis does not show fibrillation; rarely, it is possible to record some fasciculations, and MUPs are generally normal but short, small MUP can be present. A steroid myopathy is more commonly induced by a prolonged prescription for the treatment of inflammatory disorders. This can happen during the treatment of a PM and can induce some diagnostic error. The EMG findings are habitually normal since there is the selective atrophy of type 2 muscle fibers and a biopsy is necessary.

2.5.4 Metabolic Myopathies

Glycogen and lipid are both important source of energy for muscle fibers. Therefore, disorders of their metabolism may have significant muscle involvement. There are several glycogen storage diseases and two well-known diseases (carnitine deficiency and carnitine palmitoyltransferase deficiency) of lipid metabolism that induce weakness, hypotonia, and sometimes respiratory insufficiency in patients of different age. Unfortunately, EMG examination can be normal or not specific for most of these diseases, with the exception of two glycogen storage forms (acid maltase deficiency-glycogenosis II or Pompe disease and myophosphorylase deficiency-glycogenosis V or McArdle disease). In all Pompe disease forms, needle EMG shows a prominent spontaneous activity with fibrillation potentials, CRD, and myotonia discharges without clinical myotonia. Myotonia discharges origin very often from a single muscle fiber [28]. Spontaneous activity is widespread in infantile and childhood onset, while in adult form it must be investigated in proximal and paraspinal muscles [19]. McArdle disease is characterized by painful muscle contracture after a vigorous exercise that shows electrical silence at needle examination. This finding is different from all other diseases with painful cramp, where an intense electrical activity can be recorded. The contracture can also be induced by a high-frequency (50 Hz) repetitive stimulation of a motor nerve, but this painful procedure is not recommended.

2.5.5 Congenital Myopathies

Congenital myopathies are a group of clinically and genetically heterogeneous muscle disorders, which cannot be distinguished from each other by means of the neurophysiological examination. Some recent observations have shown that among the centronuclear myopathy in the adult onset form mutations were identified in DNM2 gene [29], and some of patients showed CRD at needle examination (personal observation).

2.5.6 Myopathies with Myotonic Discharges

Myotonic discharges with or without clinical myotonia can be observed in dystrophic (DM1 and DM2) and in congenital myotonias which include some channelopathies. Myotonia on needle EMG is the electrophysiologic hallmark of myotonic dystrophies. The discharges are more easily obtainable in distal and proximal muscles in DM1 than DM2 and tend to be classically waxing and waning in DM1 and waning only in DM2. Moreover, myotonic discharges are longer in DM than in congenital myotonias. However, both in dominant (Thomsen disease) and recessive (Becker disease) congenital forms, the discharges are very frequent and at times it is impossible in the analysis of single MUPs. In congenital paramyotonia, cold temperature and exercise exacerbate myotonia. This paradoxic myotonia is more easily seen during hand grip or eye closure [30, 31]. Sodium channel myotonias could be distinguished from other congenital myotonias using the short-exercise protocol [21].

2.5.7 Myasthenia Gravis

MG is an autoimmune disease caused by the presence of antibodies against components of the muscle membrane localized at the NMJ. In most cases, the autoantibodies are against the acetylcholine receptor (AChR). Recently, other targets have been described such as the MuSK protein (muscle-specific kinase) or the LRP4 (lipoprotein-related protein 4) [32–34].

RNS demonstrates an abnormal decrement in a facial or shoulder muscle in 70–80 % of patients with generalized MG and in only 50–60 % of patients with ocular MG. However, in patients with MuSK-positive MG, RNS studies are frequently normal in commonly examined muscles, and testing the most severely involved muscles to detect a decremental response may be useful. SFEMG demonstrates abnormal jitter in at least one muscle in 99 % of patients with generalized MG and in 97 % of those with ocular MG. Increased jitter and blocking frequently are found in muscles in which no decrement is detected on RNS. Unlike RNS, SFEMG cannot differentiate presynaptic from postsynaptic disorders. However, in MG characterized by a postsynaptic defect, the rapid firing rate of MU increases the jitter, while in presynaptic disorders (LEMS, botulism), jitter increases at slow firing rates and decreases at fast rates.

2.5.8 Congenital Myasthenic Syndromes (CMS)

CMS are a heterogeneous group of genetically determined structural disorders of the presynaptic, synaptic, and postsynaptic element of the NMJ. Decremental response is absent in asymptomatic CM with episodic apnea and is absent at rest but elicited by 10 Hz stimulation (protracted for 5 min) in congenital choline acetyltransferase (ChAT) deficiency. Decreased amplitude of CMAP after 10 Hz RNS for 5 min may persist up to 30 min.

Lastly, in slow-channel syndrome, there is a peculiar repetitive CMAP response to single stimulus. This response is typically observed in the small muscles of the hand and foot and is abolished by RNS at 10 Hz [6, 35].

2.5.9 Lambert-Eaton Myasthenic Syndrome

Electrodiagnostic studies in LEMS are exemplificative of presynaptic disorder of NMT. LEMS is a rare autoimmune disorder due to antibodies against presynaptic voltage-gated calcium channels; most of patients with LEMS have an underlying malignancy. The most striking electrophysiological features are a reduction in the basal CMAP amplitude after single stimulus and a marked postactivation facilitation following a brief period (generally are sufficient 10 s) of maximal voluntary contraction or high-frequency stimulation (20–50 Hz for 5–10 s). Generally, CMAP amplitude increases greatly (over 150–200 %).

Decremental response to slow stimulation rates before and after the phase of facilitation can be observed as well [5, 36].

2.5.10 Botulism

Botulism is a rare and potentially fatal disease caused by toxin produced by the bacteria *Clostridium botulinum*. Botulin toxin cleaves some of the SNARE proteins inhibiting or reducing the release of ACh into the synaptic cleft. The electrodiagnostic abnormalities are quite similar to those observed in LEMS. However, the degree of facilitation is usually less marked than that observed in LEMS (>60 %). Moreover, facilitation may be initially absent in adult in whom facilitation may require more prolonged high-frequency stimulation (up to 20 s). Postactivation exhaustion is not seen in botulism [6].

Highlights

Motor unit potentials in myopathies are generally shortened and of polyphasic shape. However, the most frequent finding of needle EMG in myopathies is the increased variability of MUPs.

Some fibrillation potentials can be found in most myopathies, but they are more frequent in sIBM, acute necrotizing myopathy, and polymyositis.

CRD are present when some hyperexcitable muscle fibers act as pacemaker with ephaptic transmission to near fibers. This happens more frequently in Pompe disease and sIBM.

Cramps are associated to a florid electrical activity, while muscle contractures (McArdle disease) are electrically silent.

A reduced CMAP amplitude in a patient with fatigability must induce the suspicion of a presynaptic disorder.

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Imaging of the Muscle

3

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3.1 Introduction

In the last decade, a growing interest for muscle imaging as a diagnostic tool in the evaluation of patients with neuromuscular disorders has been evident [1, 2].

Although ultrasonography is readily available, inexpensive, quick to perform, and useful in detecting pathological echogenicity within muscle tissues as well as muscle atrophy or hypertrophy [1, 3], magnetic resonance imaging (MRI) has become the modality of choice in the diagnostic phase of muscle disorders as it is not operator dependent and offers a superior tissue contrast even for deeper muscles [1, 4, 5].

MR imaging is currently an excellent noninvasive tool which is used in identifying muscle diseases (by showing suggestive and, sometimes, specific different patterns of muscle involvement) and in defining the extent of muscle damage [5, 6]. Moreover, muscle MRI has proven to be very useful in monitoring disease progression and assessing efficacy of therapy [7].

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To date, muscle imaging has been not extensively applied in acquired muscle diseases, except for *inflammatory myopathies*, in which it has been more often considered prior to obtaining a muscle biopsy in order to select the correct site to biopsy.

In this chapter, we summarize current knowledge on muscle imaging techniques and briefly discuss the radiological pictures in the main acquired myopathies, as dermatomyositis, polymyositis, and inclusion body myositis.

3.2 Magnetic Resonance Imaging

The cardinal radiological abnormalities which should be searched on a muscle MRI of a patient with a suspected neuromuscular disorder are both volume and structural changes.

Volume abnormalities consist in atrophy, hypertrophy, or pseudohypertrophy.

Atrophy is a reduction of the volume of the muscular bulks and can be easily detected by MRI which becomes particularly useful in identifying selective atrophy of muscles located in the immediate proximity to normal muscles in the same functional group (i.e., the rectus femoris as the only affected muscle among the quadriceps components).

MRI easily detects real *hypertrophy*, which is defined as an increase in muscle volume with maintenance of its normal structure, and distinguishes it from *pseudohypertrophy* which is a muscle volume increase due to the presence of adipose and/or connective tissue substituting muscle fibers; in the latter case, MRI shows an increase in volume associated with structural disruption of muscle tissue (Fig. 3.1).

Adipose infiltration and *edema*, defined as increased extracellular and/or intracellular water, are the main structural changes detectable by T1- and T2-weighted MRI sequences.

Adipose intramuscular replacement is detectable by T1-weighted sequences (Fig. 3.2) in which fat has a high signal because of its short relaxation time, differently from muscle tissue [8, 9].

T2-weighted images may be used in detecting both intramuscular edema and fat infiltration (Fig. 3.3). Both water and fat have longer T2 relaxation times than healthy muscle, thus explaining the brightness of muscle tissue on T2 sequences when it is affected by either these conditions [8, 9].

Sometimes, detection of edema can be hidden by an increase in intramuscular fat. Fat-suppressed T2-weighted sequences show a hyperintensity which is commonly attributed to muscle edema.

However, the exact correlates at the tissue level are still poorly understood. Moreover, increased T2 times have been documented also in the healthy muscle after exercise due to a number of proposed mechanisms including water shift from intra- to extracellular space and increase in vascular fluid volumes and/or in the proportion of "free" water to macromolecular "bound" water. It has also been described in cases of abnormal cellular infiltrate (lymphoma, bacterial myositis), rhabdomyolysis (sport-related injuries, trauma, diabetic infarction, metabolic myopathies stress-exercise related, drug and alcohol abuse), and subacute or chronic denervation [10, 11].

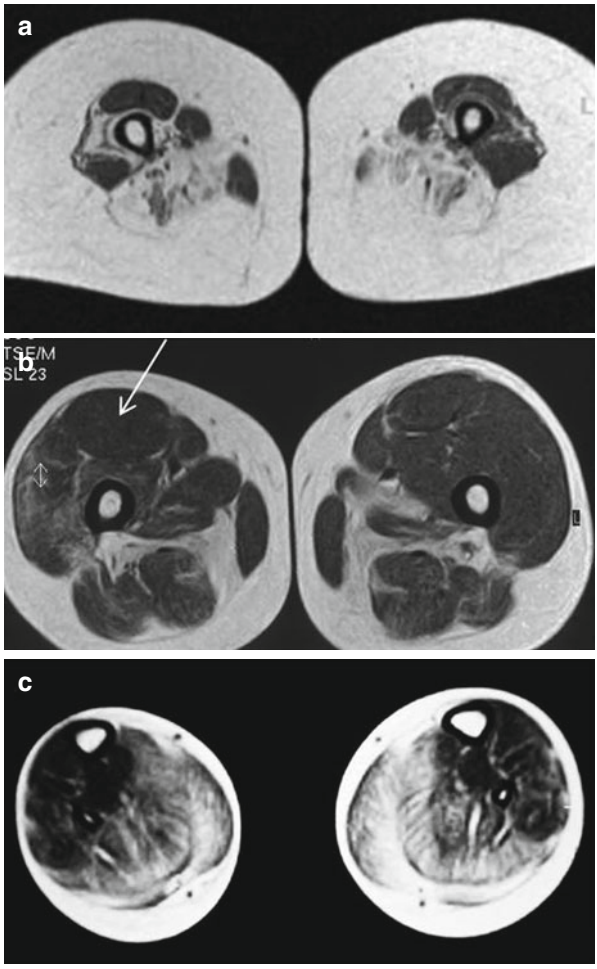

Fig. 3.1 Axial T1-weighted images at the level of the thigh (**a**, **b**) and leg (**c**) showing examples of muscle atrophy (**a**), hypertrophy (**b**), and pseudohypertrophy (**c**). (**a**) Shows increase of the subcutaneous adipose tissue and diffuse atrophy of all muscle bulks, associated with adipose substitution mainly in the posterior compartment, bilaterally, and at the level of the right vastus intermedius muscle. (**b**) Shows right quadriceps atrophy and adipose substitution, together with the selective ipsilateral hypertrophic rectus muscle (*arrow*) which maintains its normal structure. (**c**) Shows volume muscular increase of soleus, medial, and lateral gemini bilaterally due to the presence of adipose and connective tissues substituting muscular fibers, detectable as diffuse hyperintensity

To date, *STIR* (*short T1 inversion recovery*) images are preferentially used in order to better distinguish muscle edema from fat deposition as they better remove fat signal and allow visualization of increased muscle water (Fig. 3.4) [9].

The recently published recommendations on muscle MRI protocol from an international consensus suggest to use axial T1-weighted images of the pelvic girdle and lower limbs with a slice thickness of 5 mm and a relatively short TR and, where possible, *whole-body MRI* (*WB-MRI*) also in coronal planes for the study of chest, face, and upper limb muscles [10].

Although visual assessment of T1-weighted images provides rapid visualization of fat replacement and has the advantage of a more immediate impact in the clinical setting, it is difficult to quantify the degree of fatty degeneration and fat content in a robust way on these sequences.

Some novel-promising MR techniques, such as three-point Dixon or parametric T2 measures, eliminate the effects of magnetic field inhomogeneity and

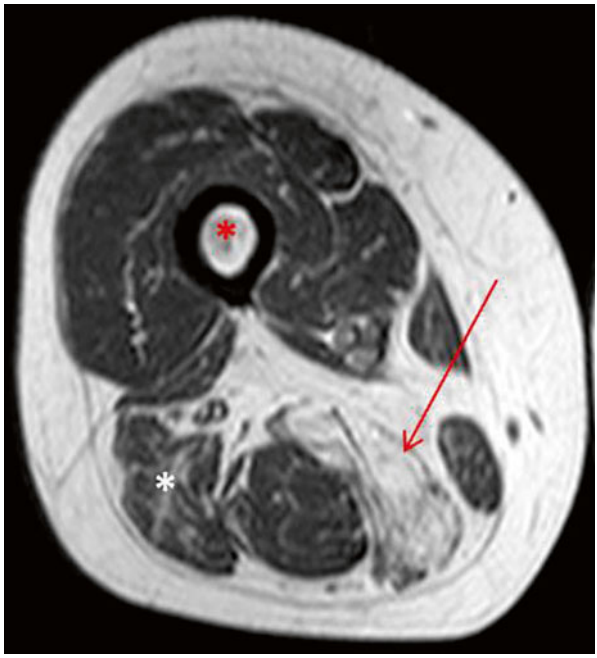

Fig. 3.2 Axial T1-weighted image at the level of the thigh showing adipose intramuscular infiltration characterized by high signal intensity at the level of the adductor magnus and semimembranosus (*red arrow*) and in a lesser extent of the long head of the biceps (*white* *). No other tissue apart from the yellow marrow bone – which can be easily distinguishable for its site in the bone (*red* *) – has the same signal intensity

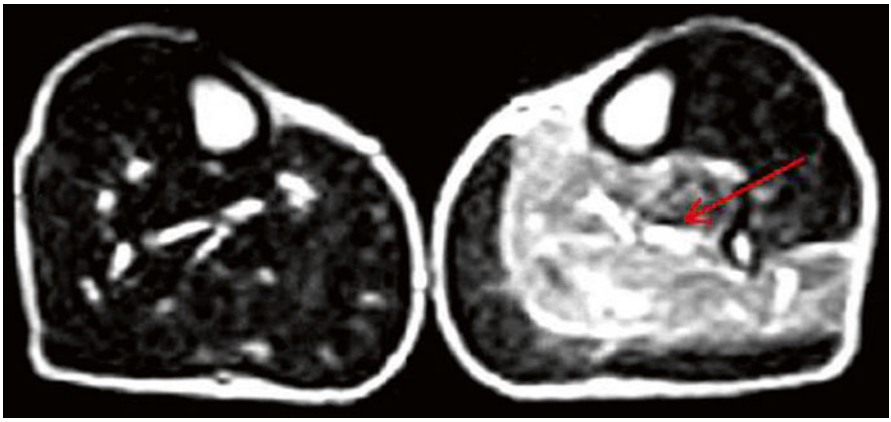

Fig. 3.3 Axial T2-weighted image of the leg showing a hyperintense edematous left soleus muscle (*red arrow*). Note that both water and fat have long T2 relaxation times, as can be seen by the signal of the subcutaneous adipose tissue

permit to correctly quantify the amount of intramuscular fat tissue, separating it from water [11]. Although post-processing of these sequences needs specific expertise, their increasing use in performing longitudinal comparison studies in multicenter settings suggests that clinical utilization of these techniques will shortly increase.

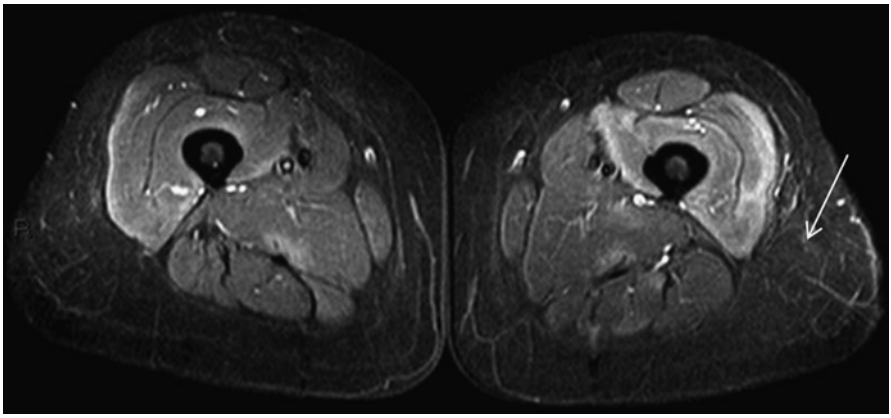

Fig. 3.4 Axial short tau inversion recovery (STIR) image of the thigh, where fat signal is suppressed, evidencing pathologic scattered edematous muscle changes of both anterior and posterior muscular compartments, mainly involving the peripheral portions of the quadriceps bilaterally. Note subcutaneous edema apparent as crisscrossing linear pattern in the subcutaneous fat (*white arrow*)

Although contrast-enhanced MRI is occasionally used, it is not recommended in clinical practice, and its diagnostic value is limited to the evaluation of septic inflammatory diseases [12].

Since fatty degeneration does not affect all muscle groups with the same extension and severity and specific muscles or muscle groups can be electively spared or specifically involved in different clinical conditions, MRI has proven to be very useful in identifying specific patterns of distribution of the pathological process.

Typical or suggestive patterns of selective muscle involvement were described in many hereditary myopathies by this "gestalt" approach which constitutes an "imaging fingerprint" of that specific myopathy. Recent literature on whole-body MRI added some useful information in the distribution pattern of the pathological process in districts as the scapular girdle and face and in congenital myopathies and glycogenosis II [13].

However, MRI has been performed in a relatively reduced number of patients for each muscle disorder, with the exception of congenital myopathies due to ryanodine receptor type 1 gene mutations and muscular dystrophies with rigidity of the spine, and further studies are necessary to better assess the MRI role in this diagnostic setting [14, 15]. Moreover, the relationship between MRI findings and some individual variables as sex, ethnicity, muscle exercising, and type of mutation in specific genes is still not deeply studied and not fully understood [8].

In clinical practice, several *MR rating scales* (usually, 4 or 5 grades ranging from normal to severe changes depending on the percentage of the involved muscle volume) are used in order to evaluate the extension of fatty degeneration and semiquantitatively assess the degree of muscle damage (Tables 3.1 and 3.2) [16–18].

Table 3.1 Modified Lamminen rating scale

Score	Description
0	Normal
1	Mild with only traces of increased signal intensity
2	Moderate with increased signal intensity in less than 50 % of the affected muscle
3	Severe with increased signal intensity in more than 50 % of the affected muscle
4	The entire muscle replaced by abnormal signal

Table 3.2 Mercuri score, MRI, T1 sequences

Score	Description
0	Normal appearance
1	Early moth-eaten appearance, with scattered small areas of increased signal
2a	Late moth-eaten appearance, with numerous discrete areas of increased signal with beginning confluence, comprising less than 30 % of the volume of the individual muscle
2b	Late moth-eaten appearance, with numerous discrete areas of increased signal with beginning confluence, comprising 30–60 % of the volume of the individual muscle
3	Washed-out appearance, fuzzy appearance due to confluent areas of increased signal
4	End-stage appearance, muscle replaced, increased density connective tissue and fat with only a rim of fascia and neurovascular structures distinguishable

The degree of fatty degeneration correlates with severity and duration of the disease. In the early stages or in mild cases, MRI scan may be normal or slightly pathological, with a selective involvement of a few muscles, while in more advanced stages, the pattern of involvement may become scarcely recognizable because muscle damage spreads to more muscles [8]. Therefore, an early diagnostic suspect and an early MRI examination may be important in order to obtain useful diagnostic informations.

Similarly to the evaluation of fatty degeneration, several rating scales have been introduced to classify and quantify muscle edema, taking into account intra-/interfascicular edema, global/segmental myoedema, percentage of muscles involved, or entity of the signal alterations [11, 19].

The spectrum of imaging findings of muscle edema ranges from focal edema involving certain parts of a single muscle to diffuse edema involving several muscle groups, as in rhabdomyolysis [10]. Edema can have a myofascial distribution (perifascicular edema) around individual muscles or muscle groups or a subcutaneous localization (soft-tissue edema) with subsequent abnormal reticulation of the subcutaneous tissues.

3.3 CT and Ultrasound Scan

CT scan has been widely used in the past years to evaluate muscle changes, in particular morphology and fatty degeneration detectable as hypodensity [5, 8, 20]. However, the soft-tissue contrast is poor, which makes it not adequate to identify

inflammatory changes, and, overall, it needs elevated doses of ionizing radiation, which has therefore allowed replacement of muscle CT scans with ultrasound (US) and magnetic resonance imaging (MRI) [6, 8].

Ultrasound is a valid low-cost and widely available approach to evaluate a suspect muscle disease [8, 21]. By evaluating echogenicity changes, it is possible to identify atrophic changes and fatty degeneration, to guide muscle biopsy, and to follow up patients [21–23]. Ultrasound scans have good resolutions, up to 1 mm, and allow dynamic studies of muscle contraction by short videos in order to examine muscle contraction and pathological muscle movements (i.e., fasciculations, myokymia) [22, 23]. However, ultrasound application in clinical practice is limited as it is operator dependent and can usually efficaciously study only superficial muscle groups.

3.4 Imaging of Dermatomyositis and Polymyositis

Inflammatory myopathies can be classified as idiopathic or secondary [24].

Adult subacute-onset idiopathic inflammatory myopathies (*IIM*) may be classified into polymyositis (PM), dermatomyositis (DM), nonspecific myositis (NSM), and necrotizing autoimmune myopathy (NAM) [25, 26]. Diagnosis is made on the basis of clinical signs, as symmetrical progressive proximal muscle weakness and worsening muscle fatigue, electromyographic findings, serum CK elevation, muscle biopsy, and assessment of myositis-specific antibodies.

Inflammation is usually present in the muscle tissue of PM, DM, and NSM patients, but it is absent in NAM [27]. However, muscle biopsy may show only nonspecific abnormalities which depends on the scattered distribution of inflammatory infiltrates in the affected muscles [28].

In this view, MRI can be helpful in distinguishing the affected muscles from the non-affected ones [27] as it allows the detection of the inflammation-related muscle edema and its extension and severity by STIR sequences [27, 28].

Muscle biopsy performed on MRI-affected muscles showed significantly more inflammatory changes than the biopsy taken from MRI non-affected muscles [29, 30]. However, in some muscle regions appearing unaffected on MRI, few inflammatory cells have been found at muscle biopsy, thus suggesting that a certain degree of inflammation is probably necessary to cause an edema observable by MRI.

In the acute phase of PM/DM, the signal intensity on MRI is associated with disease activity, and, as expected, it decreases after immunosuppressant treatment (Figs. 3.5 and 3.6). However, histological picture does not always substantially change after therapy [27, 29, 30]. This lack of clear-cut correlation between muscle biopsy findings and clinical and MRI improvement supports the notion that different mechanisms, other than the presence of inflammatory infiltrates, are involved in the pathogenesis of this group of diseases [30].

The role of imaging in the IIM workup is not limited to a triage test before performing muscle biopsy or in following up the efficacy of treatment; MRI is also an add-on diagnostic tool in patients having clinical history and presentation consistent with IIM [27].

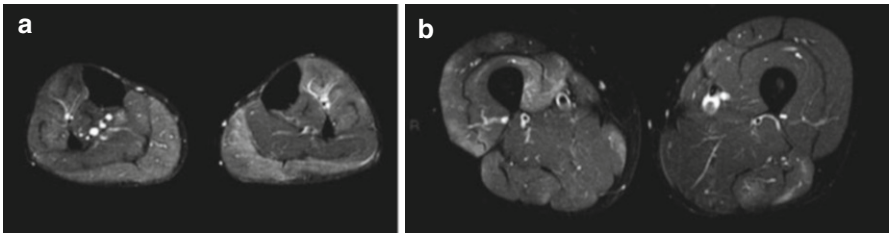

Fig. 3.5 Axial STIR images at the level of the leg (**a**) and thigh (**b**) of a patient with polymyositis in the acute phase. Diffuse scattered hyperintensities indicative of muscle edema are evident in both districts, predominantly involving both gemini and anterior compartment at the level of the legs (**a**) and the right quadriceps in the thighs (**b**)

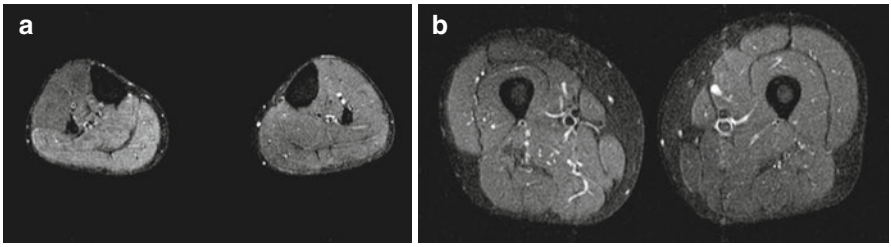

Fig. 3.6 Axial STIR images at the level of the leg (**a**) and thigh (**b**) of the same patient of Fig. 3.5 with polymyositis, after immunosuppressant treatment. Muscular edema is diffusely and markedly reduced in both districts, still slightly evident on the posterior compartment of the right leg (**a**), while in the thigh is not detectable anymore (**b**)

Interestingly, an MRI muscle hyperintensity in this group of patients has a very high positive predictive value (>80 %) if the a priori chance of having myositis is more than 60 %, even if muscle biopsy resulted not diriment (normal appearance or nonspecific findings) [27].

Although MRI can be negative if disease activity is quite low, it has been demonstrated to reduce the false-negative diagnosis when used as an add-on diagnostic test, which is a very important target for treatable diseases, even if it is at the expense of a higher false-positive rate [27, 30, 31].

The usefulness of muscle MRI has been recently tested in the juvenile form of dermatomyositis (JDM) whose course and evolution are often hardly predictable [32, 33].

A reliable *scoring system* which defines several markers of active JDM has been proposed [33]. The first marker of disease activity is the degree of muscle inflammation in four muscle groups (gluteal, hamstrings, quadriceps, and adductor) based on a four-point score (none = 0, mild = 1, moderate = 2, and severe = 3) and on the overall impression about the entire muscle group. Presence of soft-tissue and perifascicular edema is also scored.

Unfortunately, muscle or fascia MRI findings do not seem to predict clinical outcome in newly diagnosed JDM children, even if abnormal subcutaneous fat

signal appears to be significantly associated with an aggressive chronic disease course [32].

Although DM and PM share many clinical features, they have to be considered distinct diseases with different pathophysiological and histological features. Some studies conducted to assess whether this distinction can reflect also in the muscle changes observed on MRI showed that muscle edema is significantly found in the proximal regions of thigh muscles in DM, while PM MRI is predominantly characterized by fat replacement occurring mostly in the distal muscles, in their medial and distal regions [34].

WB-MRI may provide additional information to clinical evaluation and represents a promising tool to estimate total inflammatory burden, tailor treatment, and monitor its efficacy. In 2014, Malattia et al. evaluated disease activity with STIR sequences by comparing WB-MRI with clinical examination in 41 patients affected with JDM and 41 matched controls [35]. Muscle, subcutaneous tissue, and myofascial signal abnormalities were scored in 36 muscular groups and on proximal and distal extremities. WB-MRI revealed distal leg and forearm muscle inflammation undetected during clinical examination and allowed a precise assessment of subcutaneous and myofascial involvement.

WB-MRI score was higher in JDM active patients than in inactive patients and control group, and the correlation between WB-MRI muscle score and disease activity measures resulted good.

In the last years, new MRI, ultrasound, and PET techniques have been developed for the diagnosis and follow-up of IIM.

Diffusion-weighted imaging (*DWI*) may be useful in characterizing inflamed muscles by providing quantitative findings on fluid motion at different stage of disease in order to longitudinally monitor its evolution [36]. Qi et al. characterized total fluid motion within the muscle using the apparent diffusion coefficient (ADC), diffusion in the extra- and intracellular muscle compartments (D), perfusion in capillaries (pseudodiffusion), and volume fraction of capillary perfusion (f). Unaffected patient muscles have DWI coefficients equivalent to those of normal muscles. Inflamed muscles show elevated ADC and D values, while fat-infiltrated muscles have lower values than control muscles. Inflamed muscles have also lower f values, thus suggesting decreased fractional volume of capillary perfusion.

Diffusion tensor imaging (*DTI*) is also a useful method for characterizing normal and pathological muscle tissue [37]. Muscle proteins and membranous structures represent a barrier to diffusion and cause low self-diffusion coefficient of water in muscle and diffusion anisotropy. Since some changes observed in chronic myopathies, i.e., Z-line abnormalities and increased membrane permeability to water and inflammation, affect the spacing of physical barriers to free diffusion, DTI-MRI is potentially a very sensitive method to investigate such modifications and follow up the disease evolution.

Quantitative magnetization transfer (*qMT*)*-MRI* is used in characterizing the spatial distribution of the relative contents of the macromolecular and free water proton pools of biological tissues, deriving a ratio of the sizes of these two pools

(pool size ratio, PSR) [38]. It has been demonstrated that PSR may be used as a biomarker of inflammation [38, 39]. However, quantitative MRI studies in the skeletal muscle are challenged by low signal-to-noise ratio (SNR), motion artifacts, and intramuscular adipose component [38, 39]. Li et al. developed an approach for performing qMT imaging in thigh muscles using a pulsed saturation method [38]. Their data support the use of a two-parameter modeling approach in qMT imaging of the skeletal muscle in order to reduce total imaging time and to permit additional signal averaging.

Bryant et al. used a *multi-parametric MRI technique* to investigate muscle inflammation by calculating proton relaxation, DTI, qMT-MRI, and dynamic contrast-enhanced (DCE-MRI) parameters [39]. Data were acquired in a single imaging session conducted 6–8 h following the injection of λ-carrageenan, a local inflammatory agent, in eight healthy male C57BL/j6 12–14-week-old mice. T2 relaxation was elevated in the inflamed skeletal muscle, and this parameter is highly sensitive to inflammation; the global increases in T2 of the inflamed muscle in this model are largely due to the expansion of the extracellular compartment. A significant increase in ADC also occurred in the inflamed muscle, having been brought about by a general increase in diffusivity in all directions, which is likely a direct effect of the expanded extracellular space. Analysis of the qMT data revealed that the T1 of the free pool and the observed T1 both increased in the inflamed tissue, while the PSR significantly decreased as the free water pool increased. DCE-MRI data also supported observations of an increase in extracellular volume.

A *7-Tesla MRI* provided a method for noninvasively assessing inflammation and remodeling of the skeletal muscle and seems to represent an informative tool for studying in vivo immune-mediated muscle damage [40]. In a mouse model with antisynthetase syndrome, 7-Tesla MRI allowed a precise identification of the events occurring in the muscle tissue and showed that they were temporally associated with establishing autoimmunity linked to the development of anti-HisRS antibodies. Muscle changes detected by MRI paralleled edematous and inflamed areas at the histopathological studies. MRI reflected muscle damage and remodeling even if the disruption of the myofiber, as appreciated by serum creatinine phosphokinase concentration, was scarce.

Contrast-enhanced ultrasound (*CEUS*) blood flow demonstrated to be a good measure in sensitivity and specificity of perfusion in clinically affected DM and PM skeletal muscles [41]. By applying a modified model that analyzed the replenishment kinetics of microbubbles, the perfusion-related parameters (blood flow, local blood volume, and blood flow velocity) were measured, and findings were compared with muscle biopsy appearances and with the results of a 1.5-T MRI. Patients with histologically confirmed DM or PM showed significantly higher blood flow velocity, blood flow, and blood volume than those with no inflammatory myopathy signs. An increase in signal intensity on T2-weighted MR images was found in all patients with myositis.

[(*18*)*F*] *Fluorodeoxyglucose positron emission tomography* (*FDG PET*), a standard tool for evaluating malignancies, can also detect inflammatory changes.

Tanaka et al. demonstrated that [18 F] FDG uptake can discriminate PM/DM from nonmuscular diseases and is highly sensitive in detecting muscle inflammation in proximal muscles, providing useful information in the management of treatment-naive PM/DM patients [42]. The regional FDG uptake reflects muscle weakness and correlates with the infiltration of inflammatory cells at muscle biopsy.

The visual assessment of FDG uptake (vFDG) as well as the calculation of standardized uptake value (SUVmax) can improve clinical practice and provide insights into patho-mechanisms of PM/DM [43]. vFDG was observed in multiple muscle lesions with different distributions in two-thirds of the patients with PM/DM, with most lesions being symmetrical. Histological findings correlated with both the mean SUVmax and the number of vFDG-positive regions. Serum creatinine kinase levels were higher in patients with more than two vFDG-positive regions than in those with two or less regions.

3.5 Imaging of Inclusion Body Myositis

Patients with incomplete clinical presentations and/or lacking of the classical pathological features of inclusion body myositis (IBM) may be frequently misdiagnosed as a different inflammatory myopathy, especially PM, or degenerative diseases, i.e., myofibrillar myopathies, GNE myopathy, and other rimmed vacuolar myopathies [44]. Additional tools are needed to confirm IBM diagnosis, and muscle MRI has proven to be useful for the diagnostic workup, especially of patients with early disease or who lack the classical IBM pathology [44].

Upper limb imaging shows selective involvement of deep finger flexors in the forearm of patients with suspect of IBM. However, upper limb imaging is not routinely performed in the diagnostic workup of muscle diseases.

Recently, a *typical lower limb MRI muscle involvement* has been described in IBM patients, which was not found in any no-IBM patients.

The major criterion is the presence of slightly granular fatty-fibrous infiltration and/or atrophy of both quadriceps muscles in the distal portion (above the knee), particularly involving the vastus intermedius and medialis muscles, thus giving a "melted" appearance (Fig. 3.7). Involvement of the sartorius muscle is a useful additional hint, as it is usually spared in other adult-onset myopathies.

The presence of these major criteria is considered enough to define a typical case.

In uncertain cases, supporting criteria, neither necessary nor sufficient per se to define a typical case, were considered, in order of importance: (1) in the legs, the most involved muscle is the medial gastrocnemius, even if the legs can also be normal, and (2) pelvic muscles should not be heavily involved or at least less involved than thigh muscles.

In their series, Tasca et al. found a typical IBM pattern in 10 out of 17 definite IBM patients, 0 out of 2 possible IBM, and 0 out of 118 non-IBM patients. A consistent pattern was found in 6 out of 17 definite IBM patients, 2 out of 2 possible IBM, and 3 out of 118 non-IBM patients [44].

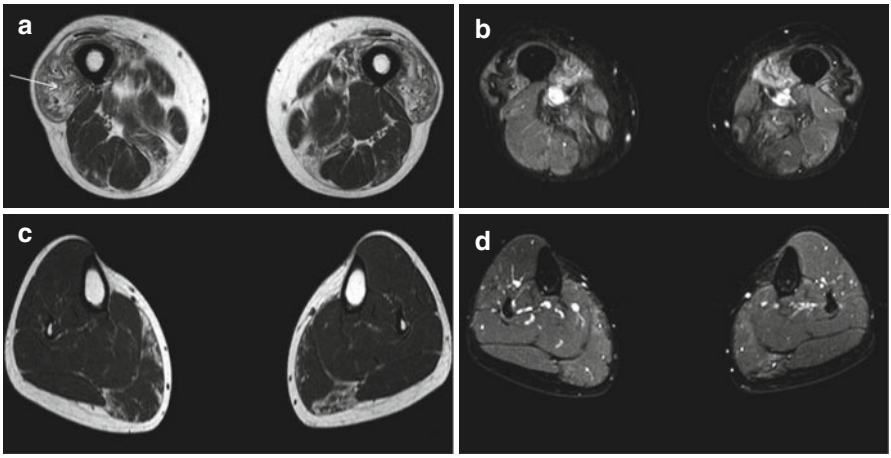

Fig. 3.7 Axial T1 and STIR images at the level of the distal thigh above the knee (**a**, **b**) and at the level of the leg (**c**, **d**) in a patient with inclusion body myositis. "Melted" appearance with slightly granular fatty infiltration and atrophy of the distal quadriceps (*white arrow*), together with abnormalities on STIR sequences mainly in the medial vasti. Note the predominant involvement of the gastrocnemius medialis at lower leg level

3.6 Imaging of Other Acquired Neuromuscular Diseases

There are only few studies on the role of imaging in other acquired neuromuscular diseases, and certainly, this topic will be a challenge for the future.

Myasthenia gravis (MG) related to antibodies to muscle-specific tyrosine kinase (MuSK) is often associated with bulbar involvement, fixed facial weakness, and tongue muscle atrophy.

In MuSK-MG patients compared with healthy controls and AChR-MG cases, MRI demonstrates thinning of the buccinator, orbicularis oris, and orbicularis oculi muscles as well as tongue areas having T1-weighted high signal [45]. An ocular-bulbar-facial-respiratory (OBFR) score was established in order to correlate MRI changes with clinical and treatment findings [45].

MRI revealed marked atrophy of temporalis, masseter, and lingual muscles with fatty replacement also in MuSK-MG patients having short duration of symptoms and still not treated with immunosuppressive therapy, thus suggesting that MuSK antibodies "per se" may be related to muscle atrophy development [46]. Otherwise, significant muscle atrophy and fatty replacement were only rarely found in the AChR-MG patients [45, 47].

Muscle MRI has been studied in a limited number of cases of *lipid-lowering agent-associated myopathy*. Although a tendency to preferential involvement of dorsal muscle groups of both thighs and legs with evidence of muscle edema, fatty replacement, or both has been observed, a distinctive MRI pattern of abnormalities was not identified [48].

In patients with *alcoholic myopathy*, high muscle signal intensities especially on T2-weighted images were observed and interpreted as indicating "pre-rhabdomyolysis" related to alcohol abuse [49] or type II fiber atrophy [50].

In *diabetic myopathy*, the anterior compartment of the thigh was involved in all the studied cases, and, interestingly, muscle infarction and necrosis was observed in 38 % of the patients [51].

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Peripheral Nerve Ultrasound

4

Luca Padua and Daniele Coraci

4.1 Introduction

Peripheral nerve ultrasound (US) is a tool complementary to clinical and electromyographic examinations. Neurophysiology provides functional data about nerves, while US supplies morphological information. In the last decades, nerve US is increasingly becoming a routine technique in neurophysiology labs for the information that can add usefulness of nerve US for diagnosis and therapeutic approach [1].

In the past, US systems were used in submarines for object detection, during the World War, and they were known as SONAR [2]. After the war, the same technology was used in medical practice as treatment tool, based on heat production by ultrasound with beneficial effects upon tissues [3]. Today this application of US is still used in physical medicine and rehabilitation.

The diagnostic use of US began during the 1940s. Development of technology, in the next 20 years, provided high-resolution images useful for diagnosis, like detection of obstetric disorders and gestation management [4]. Today US is widely employed in gastroenterology, urology, surgery, cardiology, and neurology, especially carotid and transcranial Doppler imaging [5]. Application to peripheral nervous system was less common and often overlooked.

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During the last 10–15 years, peripheral nerve and muscle imaging has become a topic of high interest. High-frequency US can assess both the nerve and muscle, and its usefulness in the diagnosis of neuropathies and muscle disorders is increasingly recognized [6, 7].

US are mechanical waves and its application in medicine is based on the properties of body tissues that transmit and reflect sound waves. Differences between the water content and structural organization of the different tissues, which represent differences in acoustic impedance, allow the creation of ultrasonographic images and the possibility to distinguish the different tissues.

The ultrasonographic beam arrives to the tissues and is reflected, scattered, transmitted, or absorbed, depending on the different properties of the tissues. The beam is produced by a transducer consisting of crystals able to vibrate when an electrical signal is applied. The same crystals can transform a mechanical vibration, when the sound waves are reflected back to the transducer, into an electrical signal. This is the piezoelectric effect. This last electric signal is translated into the visual image that can be seen on the screen of US machine. For nerve US, high-frequency probes (>12 MHz) are generally used. These high frequencies allow high image resolution but low penetration in the soft tissues [8].

US present many advantages in comparison to the other imaging techniques. US systems use small devices which can be taken to the patient's bedside; furthermore, US equipments are much less expensive than other systems. Examination time is very short, and patient safety is guaranteed; in fact no adverse effects exist and no contraindications are present for subjects with metal implants or similar. Finally, each body part can be assessed in every position with the possibility to perform dynamic scanning. These features make nerve US an extension of the clinical "eye" (Fig. 4.1).

Some disadvantages are however present, especially operator dependency and limited field of view (frequency restricts the assessable depth and bone represents an almost absolute obstacle).

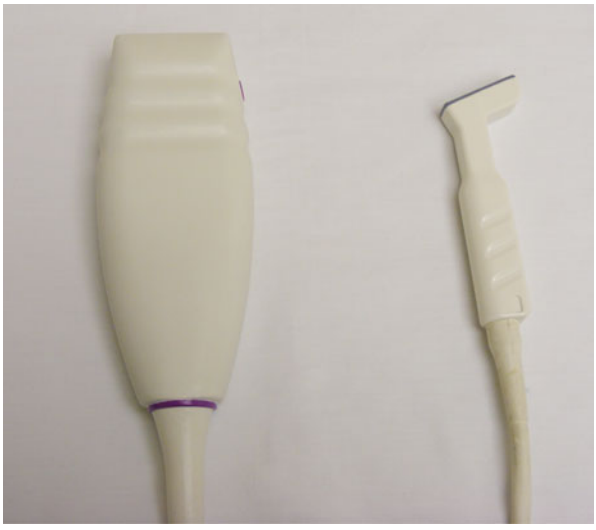

Fig. 4.1 Linear array transducers

4.2 Normal Peripheral Nerves

Peripheral nerves are mainly scanned in cross-sectional (axial) plane; the longitudinal (sagittal) plane can be used, but its utility is more limited (Fig. 4.2). Ultrasonographic nerve structure shows hypoechoic structures, the fascicles, embedded in a hyperechoic background, the epineurium. Nerves have low anisotropy, i.e. their appearance does not significantly modify with the change of transducer angle. This property is helpful for differentiating nerves from tendons, having the latter high variation of echogenicity (from hyper- to hypoechoic) [9] (Fig. 4.3).

Being made by soft tissues, the nerves are deformable, and the shape can change, from round to oval, depending on the anatomic sites and the relationships with the surrounding structures. Furthermore, the nerves are mobile, and they can change their position during dynamic US evaluation. Even if normal nerve echogenicity is quite uniform along the course, there are some points in which it can be different. In particular, when the nerve is inside an osteofibrous channel (e.g., carpal tunnel), the nerve may present a more homogeneous hypoechoic appearance (Fig. 4.4).

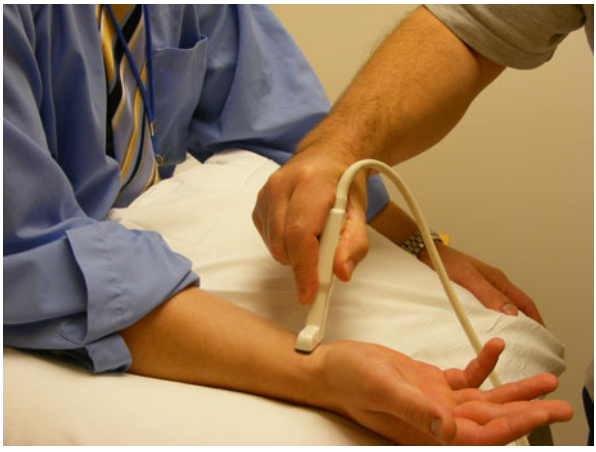

Fig. 4.2 Axial scanning of median nerve

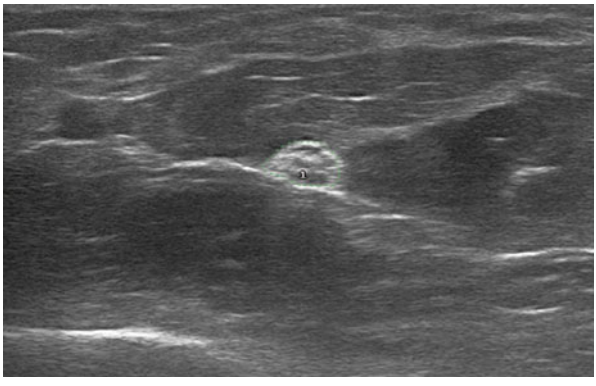

Fig. 4.3 Median nerve at forearm

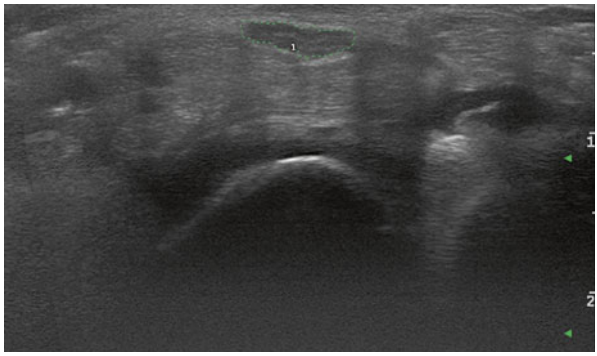

Fig. 4.4 Median nerve at wrist

The nerves of limbs can be displayed to their superficial position and absence of bone interference. The nerves in the upper limbs are more visible and assessable, because of their anatomical position. US depiction of the other nerves is not possible along the whole course. In fact, most cranial nerves and dorsal, lumbar, and sacral roots cannot be visualized, especially due to interposition of bony structures.

4.3 US in Peripheral Nerve Diseases

Nerve US has become a useful technique in different diseases of peripheral nervous system. Entrapment neuropathies, traumatic nerve lesions, nerve tumors, and immune-mediated and hereditary neuropathies are the conditions in which morphological information provided by US support the physician in diagnosis, prognosis, and treatment approach and in general patient management.

4.3.1 Entrapment Neuropathies

Nerve compressions in entrapment sites are common cases of mononeuropathies. Clinical and neurophysiological examinations are the basis for the diagnosis, but US reveals more information about the specific patient disease. US pattern of an entrapped nerve is characterized by a hypoechoic nerve presenting an increased cross-sectional area in axial plan. US is able to find the point of higher nerve suffering giving important information about the precise site of compression. This finding is crucial for the surgeon because it can avoid surgical failure and the possible relapse. Finally, US can depict the possible anatomical variants (e.g., bifid median nerve in case) [10].

4.3.2 Traumatic Nerve Lesions

The most important contribution of US in traumatic nerve lesions in this type of lesion is the possibility to distinguish axonotmesis from neurotmesis.

Neurophysiology is not able to discriminate between these two situations, but understanding the real characteristic and the degree of damage of the injured nerve allows us to recognize which kind of therapeutic approach we need. Furthermore, in cases of neurotmesis, US can measure the distance between the nerve stumps and particularly between the functional remaining parts. These data are essential for the surgical decision (suture or graft) [1].

4.3.3 Immune-Mediated Neuropathies

A focal enlargement of the nerve, often associated with a hypoechoic pattern, is usually the sign of a focal damage. In case of immune-mediated neuropathies, enlargement is the sign of inflammation and demyelination.

However, US pattern can change over the time and can indicate the phase of the disease. Recently, Padua et al. have published a study in which three main US patterns of nerve can be found in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). The first is a typical enlargement associated with hypoechoic structure, this occurs in the early stage of disease; the second pattern is characterized by enlargement and mixed hypo- and hyperechoic nerve fascicles; the last pattern is a nerve with normal dimension and hyperechoic structure. Finally, US changes can reveal the response to drug treatment: reduction in dimension and normalization of echogenicity show a good response to therapy [11].

Conclusions

Nerve US has no risks in patients of every age and situations, without, for example, the restrictions of magnetic resonance. It is able to evaluate the morphological relationships between nerve and other structures (anatomical or extrinsic) even in dynamic circumstances. The evaluation of morphological features of a nerve gives more essential information than the simple clinical and neurophysiological assessment.

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Magnetic Resonance Imaging of the Peripheral Nerve

5

Roberto Gasparotti and Massimiliano Filosto

5.1 Introduction

The diagnostic workup of peripheral neuropathies has traditionally relied on the patient's clinical history, physical examination, and electrophysiological studies [1].

Clinical and instrumental data usually provide enough information about the location, severity, as well as the etiology of the underlying nerve injury in the majority of patients. However, electrodiagnostic studies do not display the anatomical detail needed for precise localization and treatment planning; therefore imaging techniques, especially magnetic resonance imaging (MRI) and nerve ultrasound (US), are gaining an increasing role in the evaluation of peripheral neuropathies [2–4].

In conventional MRI studies, peripheral nerves are poorly visualized due to low contrast resolution between nerves, muscles, and vessels, signal intensity variability, pulsatility artifacts, and small size. These disadvantages have been overcome with the development of magnetic resonance neurography (MRN) in the 1990s [5, 6].

Ultrasound (US) is very suitable for dynamic assessment of the abnormalities of superficial peripheral nerves, such as changes in nerve caliber, continuity, and echogenicity, and represents a useful complement of clinical and electrophysiological evaluation [7], although it is more operator dependent than MRI and less effective in cases of deeply situated nerves, especially of the pelvis and lumbosacral plexus.

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5.2 Magnetic Resonance Neurography

MRN is a tissue-selective imaging technique, based on T2-weighted sequences with fat suppression, acquired with dedicated surface coils and small field of view, which is directed at identifying and evaluating specific characteristics of nerve morphology, such as internal fascicular pattern, longitudinal variations in signal intensity and caliber, and connections and relations to other nerves or plexuses [8].

The most efficient method of fat suppression is with T2-weighted short-time inversion recovery (STIR) sequences, which provide a selective suppression of the fat signal using an inversion recovery pulse of 150 ms. These sequences, however, have some disadvantages, mainly represented by poor signal-to-noise ratio and pulsatility artifacts caused by vessels. Alternative methods for fat suppression are represented by T2 spectral adiabatic inversion recovery imaging (SPAIR) or DIXON-type fat suppression, which are both characterized by a better signal-to-noise ratio, although the contrast resolution is lower [9].

In order to obtain the best compromise between spatial resolution, field of view (FOV), and acquisition time, MRN sequences should be adapted to the anatomical region and the best echo time should be carefully selected in order to obtain a satisfactory differentiation between nerves and muscles, as the signal intensity of the nerve is very sensitive to small changes [10].

Recent technological advances, such as parallel imaging, new coil design, and new sequences, together with an increasing use of 3T MR scanners, have led to the development of high-resolution MR peripheral nerve imaging, which provides significantly better depiction of peripheral nerve structures (Fig. 5.1) [11].

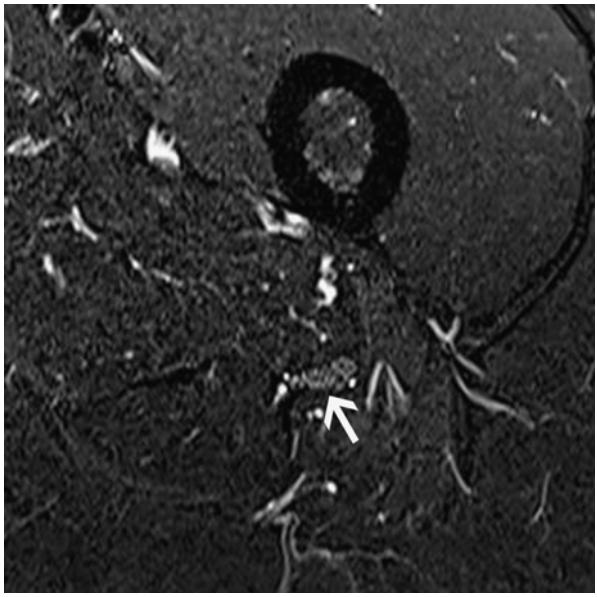

Fig. 5.1 MRN (1.5 T), axial T2-STIR section at mid-thigh. Normal subject. The right sciatic nerve (*arrow*) is moderately hyperintense compared to the adjacent muscles and its transverse fascicular pattern is clearly identifiable

Three-dimensional (3D) MRN represents a further refinement of conventional MRN. 3D sequences provide enhanced contrast between nerves and muscles and are typically acquired with isotropic voxels, therefore conferring the advantage of generating oblique and curved-planar reformations of nerve roots, peripheral nerves, and plexuses [12, 13]. This feature is particularly useful for imaging the anatomical complexity of brachial and lumbosacral plexuses which cannot be fully displayed by 2D imaging (Fig. 5.2) [14].

In MRN studies normal nerves are identifiable as rounded or ovoid structures on axial images and are typically isointense to slightly hyperintense on T2-weighted images, depending on the size of the nerve, the amount of endoneurial fluid, and degree of fat suppression, whereas they are isointense to the adjacent muscles on conventional T1-weighted images (Fig. 5.3) [15].

The epineurium appears as a thin hypointense rim and the transverse and longitudinal fascicular pattern may be identified in larger nerves such as the sciatic nerve or the median nerve at the carpal tunnel.

The signal intensity of normal nerves is strongly influenced by the amount of collagen fibers contained in the perineurium and endoneurium and their magnetic properties, which depend on the angle with the principal vector of the magnetic field, and this concept should be taken into account in the image interpretation [10].

Diseased nerves become hyperintense to muscle on MRN images and are focally or globally enlarged (Fig. 5.4) [16].

The signal intensity change is due to increased water content in the epineurial space caused by blood-nerve barrier damage, axoplasmic flow blockade,

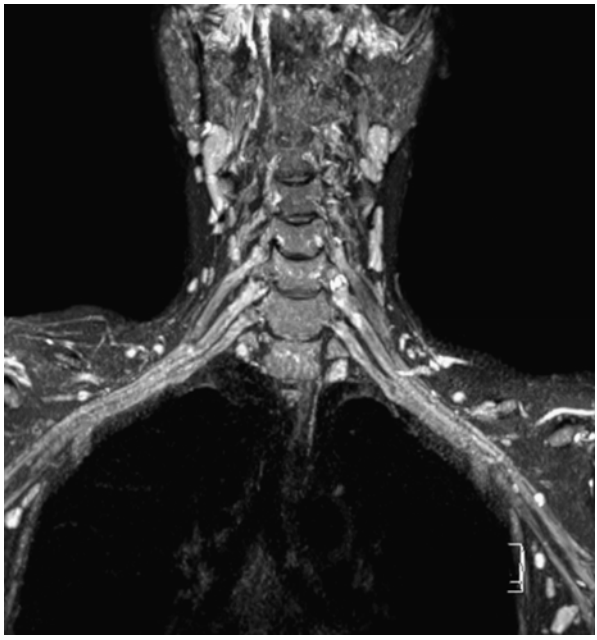

Fig. 5.2 3D MRN (1.5 T) of the brachial plexus. Oblique coronal reformat. The supra- and infraclavicular segments of the brachial plexus are simultaneously displayed in a single image

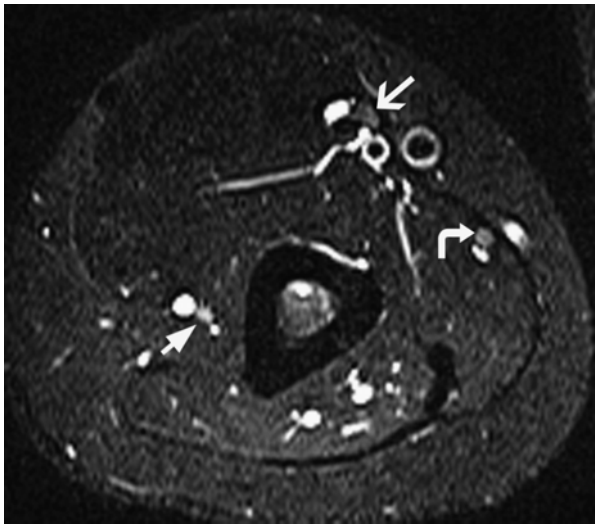

Fig. 5.3 MRN (1.5 T), axial T2-STIR section at mid-humerus. Normal subject. The median (*arrow*), ulnar (*curved arrow*), and radial (*short arrow*) nerves, which are moderately hyperintense, can be differentiated from muscles and vessels

inflammation, and distal Wallerian degeneration and is relatively independent from the etiology of the neuropathy [17].

Neuropathies with different etiologies cannot be distinguished only on the basis of signal intensity changes, as no reliable quantitative methods for evaluating the signal intensity of normal versus abnormal nerves have been developed up to now. However, a simple method based on manually drawn ROIs is represented by the calculation of nerve-to-muscle contrast-to-noise ratio (CNR) [18].

MRN has the advantage of a simultaneous exploration of nerves and muscles; therefore muscle denervation represents a useful MR sign of peripheral nerve disease (Fig. 5.4).

In the acute phase of muscle denervation, increased signal intensity can be observed in T2-weigthed sequences as early as 24 h after nerve injury and lasting for more than 2 months [19]. These denervation-related signal abnormalities are reversible and represent enlargement of the capillary bed and shift of fluid to the extracellular space. In the subacute phase, a progressive decrease of signal intensity is associated with an initial fat replacement, and in chronic phase, muscles show atrophy and sever fat replacement, which is better displayed by T1-weighted images.

The observed MR changes precede the earliest EMG findings of denervation, which are not detectable until the second week; thus MR imaging may be useful in narrowing this diagnostic gap.

Diffusion tensor imaging (DTI) is a novel technique which has been recently applied to the investigation of peripheral nerve disorders. Nerves are characterized by greater water diffusion anisotropy compared to the surrounding tissues. These techniques are sensitive to subtle changes in tissue at the microstructural level and allow measurement of nerve microstructural integrity based on quantitative parameters such as fractional anisotropy (FA) and mean diffusivity (MD) [20].

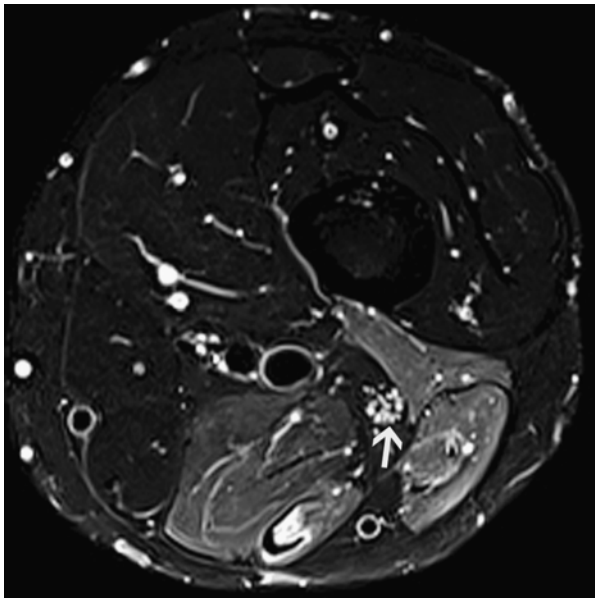

Fig. 5.4 MRN (1.5 T), axial T2-STIR section of the left thigh. Thirty-eight-year-old male with left sciatic nerve injury. Enlargement and hyperintensity of the left sciatic nerve, which is characterized by fascicular hypertrophy (*arrow*). Increased signal intensity of semimembranosus, semitendinosus, and long head of the biceps femoris, due to acute denervation

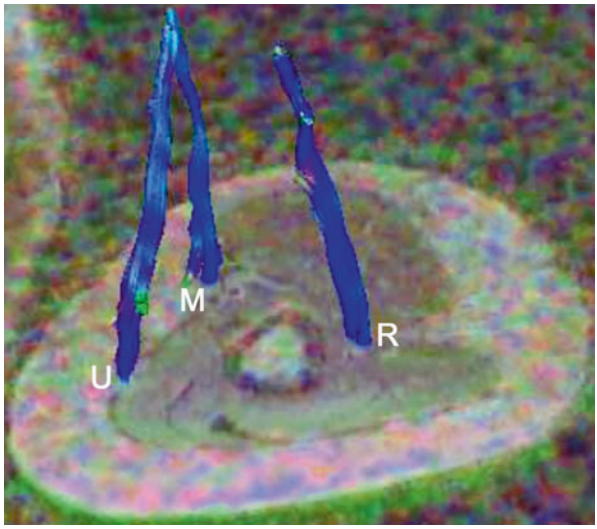

Fig. 5.5 DTI tractography (1.5 T) of median (*M*), ulnar (*U*), and radial (*R*) nerves at the arm in a normal subject

Peripheral nerve tractography is increasingly used for selective visualization of peripheral nerves. With the same approach used in deterministic tractography of the brain white matter, seed points manually drawn with the aid of a reference anatomical image allow successful tracking of the major peripheral nerves.

DTI has been extensively applied to the median nerve at the carpal tunnel and more recently to the brachial and lumbar plexus and sciatic nerves (Fig. 5.5) [21–27].

A comprehensive MRI protocol for the investigation of peripheral nerves should include MRN, which provide both structural and functional information on the nerves and muscle denervation, and T1-weighted sequences which are helpful for a precise anatomical identification of nerves and for the identification of muscular atrophy and T1-weighted sequences after contrast media administration for the evaluation of the blood-nerve barrier integrity.

MRN has been reported to be effective on the diagnostic workup of traumatic nerve injuries [28], nerve entrapment syndromes [29, 30], and nerve tumors [31]. More recently MRN has been proposed for the evaluation of hereditary and immune-mediated disorders of peripheral nerves [32].

5.3 Guillain-Barrè Syndrome

Guillain-Barrè syndrome (GBS) is a well-known inflammatory disease of peripheral nerves, including the spinal and cranial nerves, characterized by albuminocytologic dissociation and demyelinating and/or axonal involvement at electrophysiological testing.

GBS is divided into different subtypes: acute inflammatory demyelinating polyneuropathy (AIDP), which accounts for 90 % of all GBS cases in western countries; the axonal subtypes, acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN), most frequent in Asia and Japan; and the Miller-Fisher syndrome (MFS) [33].

MRI studies are usually not necessary for diagnosis, although a thorough medical assessment of patients may be needed to exclude "mimic disorders" [34].

Nerve conduction studies (NCS) and CSF analysis are important investigations that help confirming the clinical diagnosis of GBS, although NCS may be unrevealing when studying patients within days of symptom onset and CSF may be normal in the first week of the illness [35].

In the initial phase of GBS, breakdown of the blood-nerve barrier is the characteristic pathological change, which may lead to enhancement of nerve roots in MRI studies.

Although the enhancement of the intrathecal spinal nerve roots is not specific and can be seen in neoplasia and other inflammatory processes, the enhancement of only the anterior spinal nerve roots is strongly suggestive of GBS (Fig. 5.6) [36].

About 5 % of patients initially diagnosed with GBS turn out to have chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with acute onset (A-CIDP) [37].

Differentiating A-CIDP from GBS prior to relapse is challenging at the onset of the disease and has implications for treatment as well as prognosis. Electrodiagnostic studies may distinguish patients with A-CIDP from GBS; however the demonstration of cauda equina enlargement at MR imaging may be useful for the differential diagnosis.

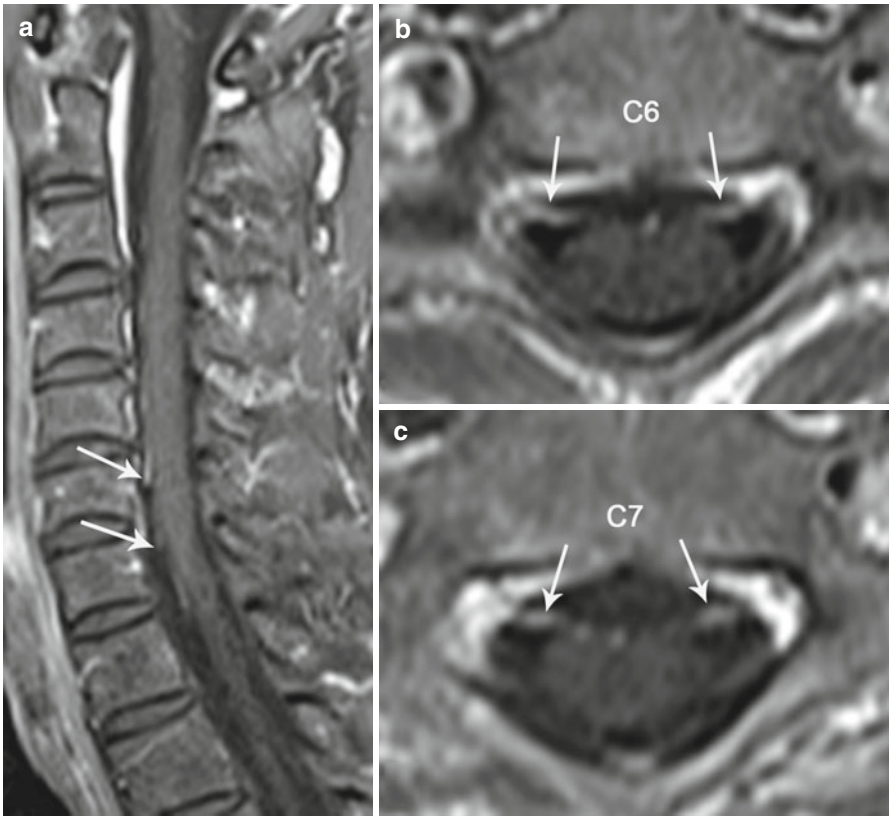

Fig. 5.6 Guillain-Barrè syndrome, sagittal (**a**) and axial T1-W sections (**b**, **c**) after gadolinium administration. Enhancement of ventral C6 and C7 nerve roots (*arrows*)

5.4 Chronic Immune-Mediated Neuropathies

5.4.1 CIDP

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated neuropathy characterized by symmetric proximal and distal weakness, with sensory loss, impaired balance, and areflexia.

CIDP include a broad spectrum of clinical phenotypes, including atypical forms with pure motor or sensory impairment or distal, multifocal, or focal distributions [38].

The diagnosis of CIDP is based on a combination of clinical, electrodiagnostic, and laboratory features, primarily directed at detecting signs of demyelination; however in clinical practice CIDP may be difficult to diagnose, especially in atypical cases. Despite the good overall sensitivity and specificity of the current electrophysiological criteria, almost 20 % of patients in CIDP cohorts do not match these criteria [39].

MRI showing gadolinium enhancement or hypertrophy of the cauda equina, nerve roots, or plexuses has been recommended as an additional supportive exam in a recent revision of the European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of CIDP [40].

The most frequent MRI finding in patients affected by CIDP is represented by bilateral and symmetric hypertrophy of both brachial and lumbosacral plexus, which is invariably associated with increased signal intensity, better displayed by MRN (Fig. 5.7).

Hypertrophy and increased signal intensity of the cervical roots and brachial plexus at MRI have been reported in 57 % of patients affected by CIDP, 75 % of whom also had also hypertrophy of the lumbar plexus [41].

Patients with nerve root hypertrophy usually have a relapsing-remitting course and a significantly longer disease duration, which may be related, according to some authors, with the process of demyelination and remyelination [41]. Similar findings of enlargement and increased MR signal intensity have been observed in the median and ulnar nerves of patients with CIDP, correlating with the site of conduction block and contrast enhancement during relapses or active progression, possibly reflecting increased water content within the nerve fascicles and disruption of the blood-nerve barrier due to the inflammatory process [42].

3D MRN has become a valuable tool for a thorough assessment of the symmetry and longitudinal extent of the disease.

Using 3D MRN techniques, Shibuya et al. showed longitudinal morphological changes from the cervical roots to the nerve trunks in the proximal arm in 88 % of patients affected by CIDP [43].

Phenotypic features can be noninvasively characterized in patients with atypical variants of CIDP using 3D MRN for a detailed evaluation of brachial and lumbosacral plexus hypertrophy and signal intensity abnormalities, which typically involve long segments with a different distribution, symmetric or asymmetric, diffuse or multifocal.

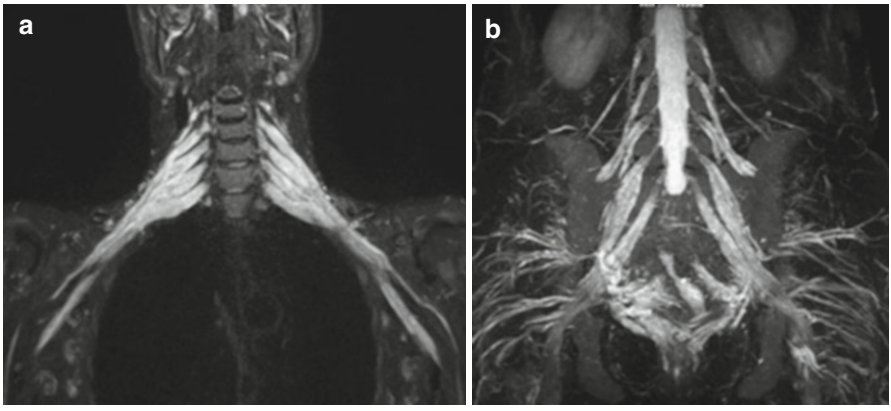

Fig. 5.7 Chronic inflammatory demyelinating polyradiculoneuropathy, 3D MRN (1.5 T), showing diffuse symmetric hyperintensity and enlargement of the brachial (**a**) and lumbosacral plexus (**b**)

Lewis-Sumner syndrome (LSS) or multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) is characterized by asymmetry, presenting as a multifocal multiple mononeuropathy most commonly in the upper limbs, accounting for 6–15 % of CIDP patients [44].

The distribution of hypertrophy in typical CIDP is symmetric and predominant in the nerve roots, with gradual normalization toward the proximal arm segments distally, whereas in MADSAM nerve hypertrophy is usually asymmetric and multifocal in the peripheral nerve trunks [43] (Fig. 5.8).

Sensory predominant CIDP occurs in 5–35 % of patients, often starting with lower limb numbness [45]. The diagnosis is typically made on the basis of demyelinating electrodiagnostic features in motor nerves, which may occur without motor signs, although patients may develop weakness at a later date [46]. This entity may be underdiagnosed at the onset of symptoms which manifest at a young age and 3D

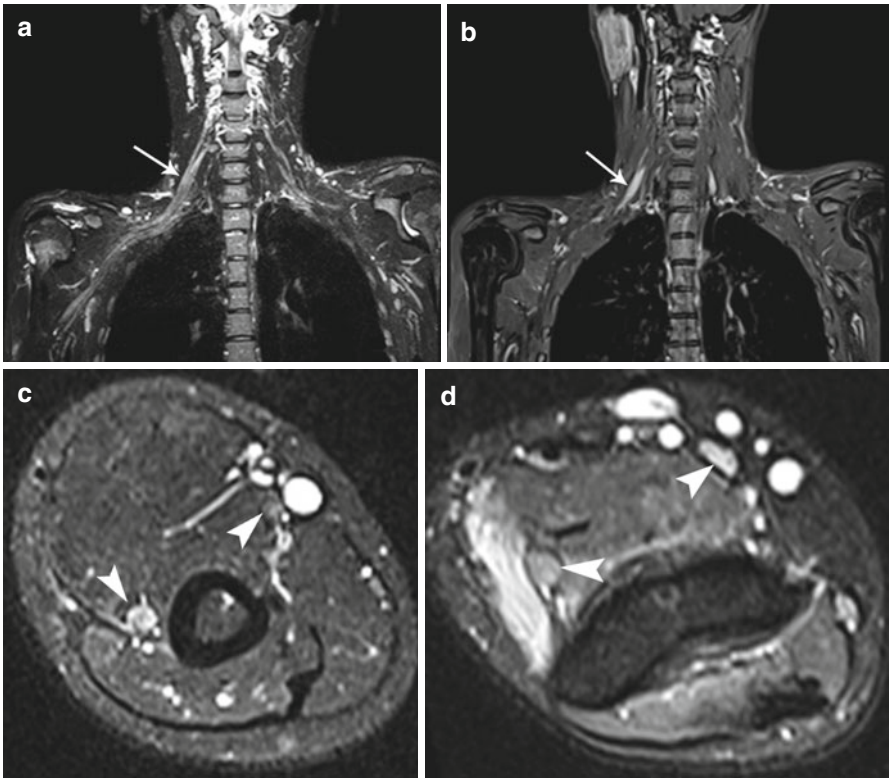

Fig. 5.8 Multifocal acquired demyelinating sensory and motor neuropathy, 3D MRN (1.5 T) of the brachial plexus (**a**), coronal T1-W section after gadolinium administration (**b**), MRN, axial T2-STIR section of the right arm (**c**, **d**). Asymmetric hypertrophy of the right brachial plexus (*arrow* in **a**), with enhancement of the right C6 nerve root and superior primary trunk (*arrow* in **b**). Hypertrophy and increased signal intensity of the right radial and median nerves (*arrowheads* in **c** and **d**)

MRN may represent a useful diagnostic tool when demonstrating symmetric hypertrophy of the brachial and lumbosacral plexus, which is comparable to the typical form of CIDP [47].

Brachial and lumbosacral plexus hypertrophy on MRI is also well documented in patients with demyelinating Charcot-Marie-Tooth disease (CMT) [48], and the differential diagnosis with CIDP, besides genetic abnormalities, can also rely on the measurement of the sciatic nerve cross-sectional area (CSA) at mid-thigh by means of MRN (Fig. 5.9) [49].

New MR techniques such as diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI) have proven to be particularly useful for the investigation of CIDP (Fig. 5.10).

High signal intensity in DWI sequences and increased values of the apparent diffusion coefficient (ADC) were detected in 55.6 % of cases in a small cohort of 13 CIDP patients, which might be strictly correlated with proliferating layers of Schwann cells and increased endoneurial collagen surrounding the axons [50].

Kakuda et al., investigating 10 CIDP patients with 3T DTI, found significantly reduced FA values in the tibial nerves of patients compared to controls and an association between FA and the amplitude of action potentials in electrodiagnostic tests, suggesting a correlation with axonal damage more than with the degree of demyelination [51].

5.4.2 Multifocal Motor Neuropathy

Multifocal motor neuropathy (MMN) is a chronic, slowly progressive immune-mediated neuropathy, characterized by progressive, predominantly distal, asymmetric limb weakness, mostly affecting upper limbs, minimal or no sensory impairment, and the presence of multifocal persistent partial conduction blocks (CB) on motor nerves [52]. Increased levels of serum IgM antibodies to the ganglioside GM1 are another typical feature of the disease.

MRI may be of value in the differential diagnosis with MMN, classified as a variant of CIDP in the past and now considered a different disease [53].

A recent revision of the European Federation of Neurological Societies/Peripheral Nerve Society on Multifocal Motor Neuropathies (MMN) also included MRI as a supportive criterion for the differential diagnosis with other neuropathies such as CIDP or multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy (Lewis-Sumner syndrome) and motor neuron disease (MND) [54].

About 40–50 % of the patients with MMN show asymmetric hypertrophy and signal intensity abnormalities or contrast enhancement on MR of the brachial plexus, and the pattern of signal alterations closely correlates with the distribution of muscle weakness (Fig. 5.11) [55].

Diffuse nerve swelling and hyperintensity of the affected nerves on the T2-weighted images are usually found in areas outside the expected confines of

entrapment neuropathy and reflect demyelination and proximal conduction blocks [56].

The clinical presentation of MMN may mimic motor neuron disease (MND), particularly in patients with predominant lower motor neuron impairment, and the

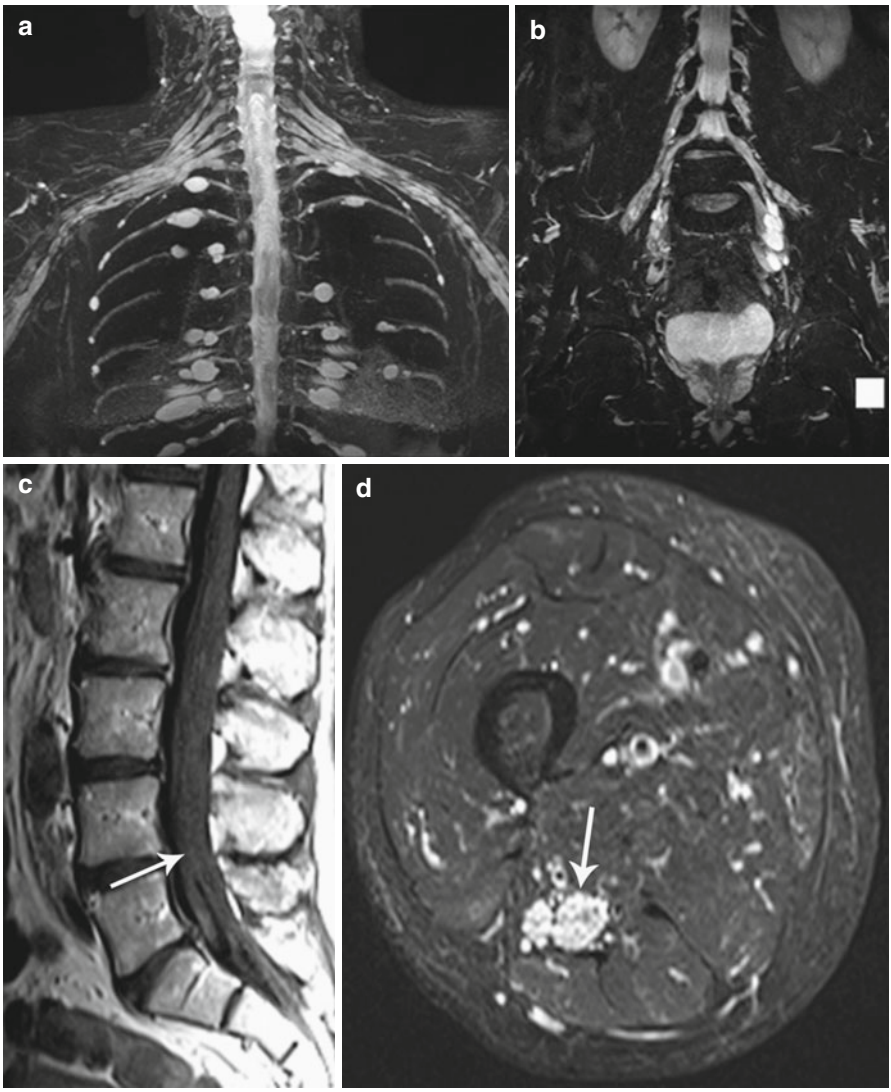

Fig. 5.9 Charcot-Marie-Tooth disease type 1A, 3D MRN (1.5 T) (**a**, **b**), sagittal T1-W section of the lumbar spine (**c**), MRN, T2-STIR section at mid-thigh (**d**). Diffuse symmetric hypertrophy and hyperintensity of the brachial plexus and intercostal nerves (**a**) and lumbosacral plexus (**b**). Hypertrophy of the cauda equina (*arrow* in **c**). Hyperintensity and hypertrophy of the right sciatic nerve (CSA = 270 mm^2) (*arrow*), with excellent visualization of the tibial and peroneal divisions

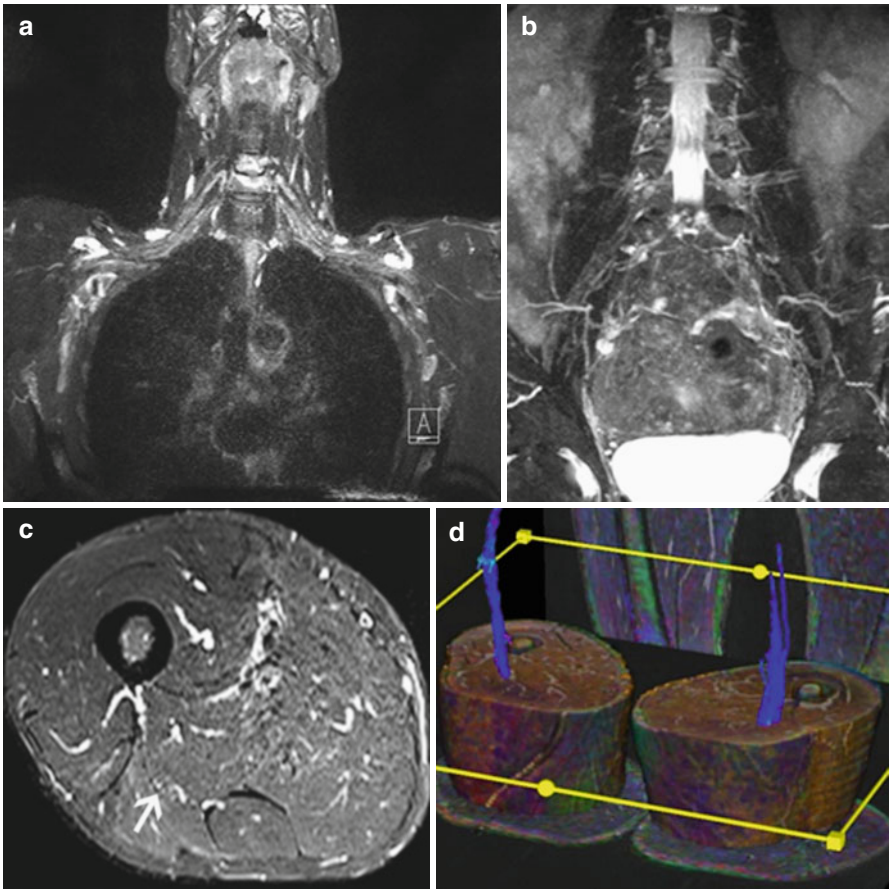

Fig. 5.10 3D MRN (1.5 T) (**a**, **b**), MRN, axial T2-STIR section of the right thigh (**c**) and DTI tractography of sciatic nerves (**d**) in a patient with CIDP. There are no detectable abnormalities of brachial, lumbosacral plexus and sciatic nerves at mid-thigh (*arrow* in **c**). The quantitative evaluation of the microstructure of normal-appearing sciatic nerves based on DTI tractography demonstrated decreased fractional anisotropy (FA) compared to the reference values in normal subjects (0.37 vs 0.5)

differential diagnosis is important, as the prognosis and treatment of these diseases are different.

MRI can be used to help differentiate between MMN and MND, with brachial plexus MRI being normal in the latter [57].

Axonal multifocal motor neuropathy is a rare entity, which was first described in 2002, and is characterized by a slowly progressive multifocal motor phenotype with neither conduction blocks nor other features of demyelination [58].

MR neurography has been recently reported to be helpful in the diagnostic workup of the axonal form of MMN, showing mildly increased signal intensity and size of the involved nerves at the arm [59].

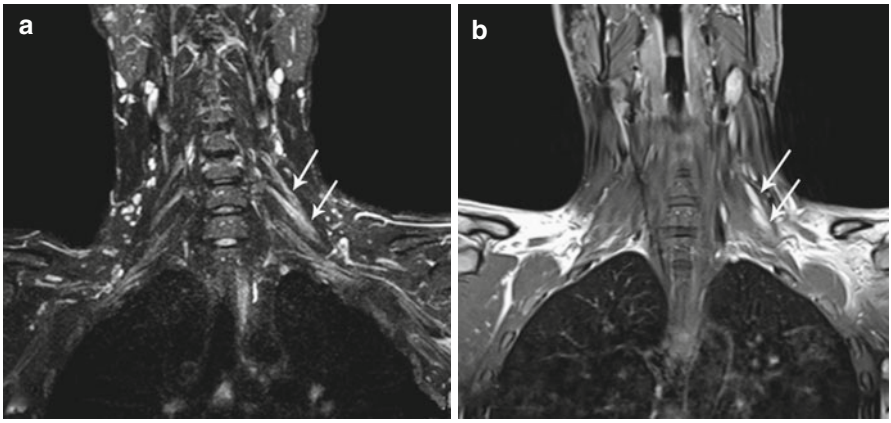

Fig. 5.11 Multifocal motor neuropathy, MRN (1.5 T), coronal T2-STIR section of the brachial plexus (**a**), coronal T1-W section after gadolinium administration (**b**). Asymmetric hypertrophy and hyperintensity of the left brachial plexus (*arrows* in **a**) with enhancement of C5 and C6 nerve roots (*arrows* in **b**)

5.5 Diabetic Polyneuropathy

Diabetic peripheral neuropathy (DPN) is the most common form of the diabetic neuropathies seen in either type 1 or type 2 DM, with similar frequency. DPN is a common late complication of diabetes and has been recently defined as a symmetric, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvascular alterations as a result of chronic hyperglycemia exposure and cardiovascular risk covariates [60].

Recently high-resolution 3T MRN has been applied to a relatively small group of diabetic patients with distal symmetric polyneuropathy with the aim to detect intraneural signal intensity abnormalities in sciatic nerves [61]. Multifocal fascicular lesions within the proximal tibial and peroneal divisions of the sciatic nerves within proximal nerve trunks were detected in patients with higher neuropathy deficit score (NDS), demonstrating a possible role of high-resolution in vivo MRN in the evaluation of diabetic nerve injury.

DPN also include radiculoplexus neuropathies which affect roots, plexus, and individual nerves in the cervical, thoracic, or lumbosacral segments.

Diabetic lumbosacral radiculoplexus neuropathy (DLRPN), which is characterized by debilitating pain, weakness, atrophy of the proximal thigh muscles, and abnormal protein content in CSF, is the best studied subtype [62].

The occurrence of a cervical diabetic radiculoplexus neuropathy (DCRPN) sharing many of the clinical and pathological features of DLRPN has also been recently demonstrated [63].

MR imaging is very useful in demonstrating increased signal intensity in nerve roots and trunks which is invariably associated to denervation changes into the affected muscles in both forms (Fig. 5.12).

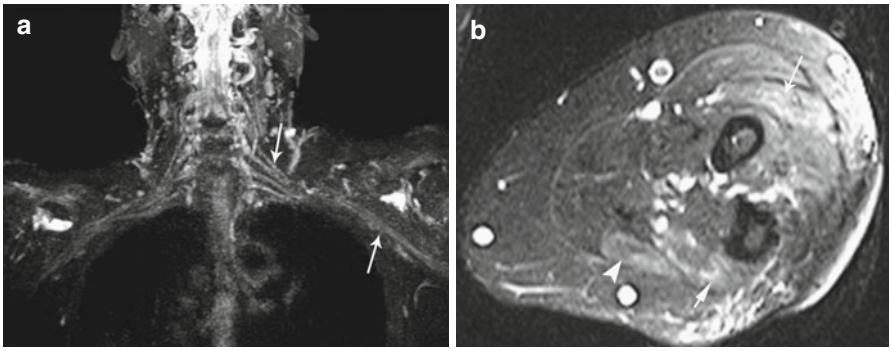

Fig. 5.12 Diabetic cervical radiculoplexus neuropathy in a 64-year-old female with type 2 diabetes, 3D MRN (1.5 T) (**a**), MRN, axial T2-STIR section at left mid-forearm (**b**). Mild enlargement and hyperintensity of the left supra- and infraclavicular brachial plexus (*arrows*). Denervation changes into the left extensor carpi ulnaris (*short arrow*), extensor digitorum (*arrowhead*), and extensor carpi radialis (*long arrow*)

5.6 Amyloid Neuropathy

Amyloid neuropathies occur in a context of hereditary or acquired amyloidosis. They present usually as severe and progressive polyneuropathy involving sensory, motor, and/or autonomic fibers and carry a poor prognosis [64].

Acquired amyloid neuropathy is almost exclusively represented by immunoglobulin light-chain amyloidosis (AL) and is frequently associated with renal manifestations and monoclonal protein in serum or urine. Peripheral neuropathy occurs in about 35 % of cases of AL but is a rare presenting symptom [65].

On MR imaging both focal amyloidoma and diffuse enlargement of unilateral/bilateral nerves with associated multifocal lesions have been reported [66, 67]. The lesions most commonly involve segments of the lumbosacral plexus or the sciatic nerve and are characterized by variable contrast enhancement of the affected nerves.

Transthyretin familial amyloid polyneuropathy (TTR-FAP) is the most common form of inherited amyloidosis. Endemic areas of TTR-FAP are Portugal, Japan, Sweden, and Brazil. Patients with FAP may experience different patterns of neuropathy including focal neuropathies, sensorimotor polyneuropathy, autonomic neuropathy, or combinations of the three. The median nerve at the wrist is a common and early site of involvement in FAP [68].

The diagnosis relies on a positive family history and requires TTR gene analysis showing Met30TTR mutation and positive labial salivary gland biopsy (LSGB) for amyloidosis [69].

High-resolution 3T MRN has been recently shown to be able to identify and quantify the distribution of peripheral nerve injury in TTR-FAP patients within the fascicles of the sciatic nerves from proximal to distal, even before the manifestation of symptomatic disease in asymptomatic gene carriers, in whom imaging detection may precede clinical and electrophysiological manifestation [70].

5.7 Sarcoidosis

Sarcoidosis is a granulomatous, multisystem disease of unknown etiology. Approximately 3.5–5 % of the patients with sarcoidosis have involvement of the central and peripheral nervous system (neurosarcoidosis), although peripheral nerve manifestations are rare and usually seen late in the disease.

Acute or chronic peripheral neuropathy occurs in about 2–40 % of patients with neurosarcoidosis. The most common form is represented by symmetric axonal sensory motor polyneuropathy. Other patterns include mononeuritis multiplex and Guillain-Barrè-like syndrome [71].

Sarcoid granulomas locate themselves in the perineurium and epineurium, while the endoneurium is mostly spared.

Although CNS sarcoidosis can be diagnosed using contrast-enhanced MR imaging [72], the diagnosis of PNS sarcoidosis is more difficult.

MRN has been reported as a useful tool in the diagnostic workup of sciatic nerve sarcoidosis, which can manifest as a mass within the sciatic nerve (sarcoid granuloma), characterized by low signal intensity in T2-weighted images and marked enhancement after contrast administration [73].

Key Points

Magnetic resonance neurography is an imaging technique, directed at identifying and evaluating specific characteristics of nerve morphology, such as internal fascicular pattern, and longitudinal variations in signal intensity and caliber.

Advanced 3D MR neurography techniques allow oblique and curved-planar reformations along the course of peripheral nerves and are particularly suitable for imaging brachial and lumbosacral plexus.

Diseased nerves are hyperintense to muscle on MRN images and appear focally or globally enlarged. The signal intensity variations are not specific and are due to increased water content in the epineurial space, blockade of axoplasmic flow, inflammation, and distal Wallerian degeneration.

Muscle denervation imaging is part of an MR neurography examination and represents a useful sign of peripheral nerve disease.

The most frequent MRI finding in patients affected by CIDP is represented by bilateral and symmetric hypertrophy and hyperintensity of both brachial and lumbosacral plexus, better displayed by MR neurography.

Atypical variants of CIDP and MMN can be noninvasively characterized with 3D MRN of the brachial and lumbosacral plexus, showing symmetric or asymmetric longitudinal morphological changes from roots to nerve trunks and variable contrast enhancement.

MRI of the brachial plexus can be used in the differential diagnosis between MMN and MND, with MRI being normal in the latter.

In diabetic cervical and lumbosacral radiculoplexus neuropathies, MR neurography is useful in demonstrating increased signal intensity in nerve roots and trunks which is invariably associated to denervation changes into the affected muscles.

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Part II

Clinical Myology Entities

The Spectrum of Inflammatory Myopathies: Dermatomyositis, Polymyositis, Necrotizing Myositis, and Inclusion-Body Myositis

6

Marinos C. Dalakas

6.1 Introduction

Since 1991, when a major review on inflammatory myopathies was published [1], there has been tremendous progress in our understanding of these disorders. Although they still comprise a heterogeneous group of muscle diseases, unique clinical, histologic, and immunopathologic characteristics have emerged to classify them in four distinct subsets, namely, *dermatomyositis* (*DM*), *polymyositis* (*PM*), *necrotizing autoimmune myositis* (*NAM*), and *inclusion-body myositis* (*IBM*) [2–4]. Another subtype, preferably called *overlap myositis*, is currently increasingly recognized and seems to be a fifth distinct subset [1]; these patients show histologic features similar to DM but without ever having a skin rash; often have antisynthetase antibodies, as discussed later; and probably exhibit distinct nuclear actin filament aggregates [5]. Identification of the correct subtype and distinction from disease mimics are important because each subset has different prognoses and responses to therapies [1–4] as, overall, DM responds better than PM and PM better than NAM while IBM remains difficult to treat. The chapter reviews current knowledge in the field; highlights how best to avoid erroneous diagnoses; describes the main clinical, histopathologic, and immune features; and offers a practical update on therapies.

6.2 General Clinical Features Relevant to All IM

Patients with IM experience difficulty with tasks requiring the use of proximal muscles, such as getting up from a chair, climbing up steps, or lifting objects [1–4, 6]; tasks requiring the strength of distal muscles, such as buttoning or holding objects like a pen

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or golf clubs, are affected early in IBM but only in advanced cases of PM, DM, and NAM. Ocular muscles are spared in all subtypes and, if affected, the diagnosis of IM should be questioned. Facial muscles are unaffected in DM, PM, and NAM but they are commonly involved in IBM even early in the disease [2–4]. In all subsets, pharyngeal and neck extensor muscles can be affected, resulting in dysphagia or difficulty holding up the head. In advanced and rarely acute cases, respiratory muscles may be affected. Extramuscular manifestations may also occur and include (a) systemic symptoms, such as fever, malaise, arthralgias, and Reynaud's phenomenon when associated with another systemic disease or with antisynthetase antibodies (the so-called Jo-1 syndrome); (b) cardiac arrhythmias or ventricular dysfunction if the cardiac muscle is rarely affected; and (c) breathing difficulties rarely due to respiratory muscle involvement but more often due to interstitial lung disease as often seen with antisynthetase antibodies [1].

6.3 Dermatomyositis

Seen in both children and adults, DM presents with distinct skin manifestations in face and extremities, accompanying or preceding muscle weakness. These changes include a heliotrope (blue-purple) rash on upper eyelids with edema; an erythematous rash on the face, knees, elbows, malleoli, neck, anterior chest (in V sign), back, and shoulders (in shawl sign) and knuckles with a violaceous eruption (Gottron's rash) that evolves into a scaling discoloration. Dilated capillary loops at the base of the fingernails, irregular and thickened cuticles, and cracked palmar fingertips (mechanic's hands) are characteristic [1–7]. Subcutaneous calcifications, sometimes extruding to the surface causing ulcerations and infections, may occur especially in children but less often today owing to early initiation of better therapies. Dermatomyositis can be limited to the skin if strength appears normal (*amyopathic dermatomyositis*), although there is often subclinical muscle involvement [2–4]. In children, an early symptom is "misery," defined as an irritable child with red flush on the face, fatigued, and reluctant to socialize [2–4].

Dermatomyositis may overlap with systemic sclerosis and mixed connective tissue disease [1–4]. In up to 15 % of adult patients, there may be an underlying malignancy, most commonly ovarian, breast, or colon cancer, melanoma, non-Hodgkin lymphoma, and nasopharyngeal cancer in Asians, necessitating a thorough annual workup, especially the first 3 years from disease onset [1–4, 6, 7]. Although tumors are usually uncovered by abnormal findings in physical examination and not by extensive blind searches, whole-body PET imaging might be considered if malignancy is strongly suspected.

6.4 Polymyositis

In contrast to DM where the skin manifestations unravel the disease, polymyositis has no unique clinical features that point to disease onset. PM is rare as a stand-alone entity and very often misdiagnosed; it is most frequently encountered in patients with systemic, autoimmune, or viral diseases [1–4] and remains a diagnosis of exclusion. It is

a subacute myopathy occurring in adults who do not have rash, family history of neuromuscular disease, exposure to myotoxic drugs (d-penicillamine, zidovudine), involvement of facial and extraocular muscles, endocrinopathy, or the clinical phenotype of IBM, as described later.

6.5 Necrotizing Autoimmune Myositis (NAM)

It is a distinct and previously overlooked entity, occurring more frequently than PM [2–4]. It is seen in all ages but mostly adults and starts either acutely, reaching its peak over days or weeks, or subacutely progressing steadily resulting in severe weakness and very high CK levels. Interstitial lung disease may coexist. The disorder is most of the times autoimmune and antibody-mediated, but it may also sometimes occur after viral infections or in association with cancer. It has been suggested that may be also induced by statins but this connection may be serendipitous considering that NAM is now recognized as a common myopathy while statins are prescribed in more than 30 % of patients above 50 and more than 40 % above 60–65; further, a temporal connection with statin initiation has not been demonstrated [2, 8–10]. Up to 60 % or more of NAM patients have antibodies against signal recognition particle (SRP) or the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) [2, 9, 10], as discussed later. NAM should be distinguished from muscular dystrophies especially if encountered in young patients.

6.6 Inclusion-Body Myositis (IBM)

It is the most common and disabling IM above the age of 50 [1–4, 11–14]. It starts insidiously, over years, and progresses steadily simulating a late-life muscular dystrophy or slowly progressive motor neuron disease. Most patients will require an assistive device such as cane, walker, or wheelchair several years after onset. Although IBM is commonly suspected when a patient with presumed PM did not respond to therapy, involvement of distal muscles almost from the outset, especially foot extensors and deep finger flexors with atrophy of the forearms, frequent falls due to early involvement of the quadriceps muscle causing buckling of the knees and mild facial muscle weakness are clues to early clinical diagnosis [1–4, 11–14]. Axial muscles may be affected resulting in camptocormia or head drop.

6.7 Diagnosis

The diagnosis of the exact subset is based on the combination of clinical history, tempo of disease progression, pattern of muscle involvement, determination of serum muscle enzymes, electromyography, muscle biopsy, and, for some conditions, certain autoantibodies [2–5].

6.7.1 Serum Muscle Enzyme Levels

The most sensitive indicator is creatine kinase (CK), which is elevated in almost all IM subsets when they have active disease. The higher levels, up to thousands, are seen in NAM and the lowest (less than ten-fold in IBM). Although serum CK usually parallels disease activity, it can be normal or only slightly elevated, in several cases of active IBM as well as cases of active DM and overlap myositis reflecting pathology predominantly in the interstitial tissue and between the fascicles. Along with serum CK, glutamate oxaloacetate transaminase (GOT) and glutamate pyruvate transaminase (GPT) are also elevated, a sign sometimes erroneously interpreted as denoting liver disease leading to an investigation with liver biopsy instead of muscle biopsy. Serum aldolase may be also elevated especially if the fascia is involved as often seen in overlap myositis or myofasciitis.

6.7.2 Electromyography

This shows myopathic motor unit potentials (short-duration, low-amplitude polyphasic units on voluntary activation) and increased spontaneous activity with fibrillations, complex repetitive discharges, and positive sharp waves. These findings are useful to demonstrate active or chronic myopathy and exclude neurogenic disorders, but it is insensitive to differentiate an inflammatory myopathy from toxic or dystrophic myopathies [1–4].

6.7.3 MRI

This is increasingly utilized and, in certain clinical settings, may provide useful information about the extent and selectivity of muscle involvement, identify disease activity, and guide the selection of the most active muscle to perform a diagnostic biopsy. It is helpful in demonstrating fasciitis and in identifying the pattern of muscle involvement in IBM, especially if fat-suppression techniques are utilized to differentiate inflammation from chronic atrophy and fatty replacement. In spite of some reports that MRI can be diagnostic for IBM, it cannot distinguish these changes from dystrophies and caution should be exercised in its use as a definitive diagnostic test.

6.7.4 Muscle Biopsy

Although not always typical, muscle biopsy is the most sensitive and specific diagnostic tool because it shows features distinct for each subset, provided the biopsy site is properly chosen, the specimen is processed by an experienced laboratory, and the findings are interpreted in the context of the clinical picture [1–4, 6]. In DM, there are inflammatory infiltrates perivascularly, in the interfascicular septae

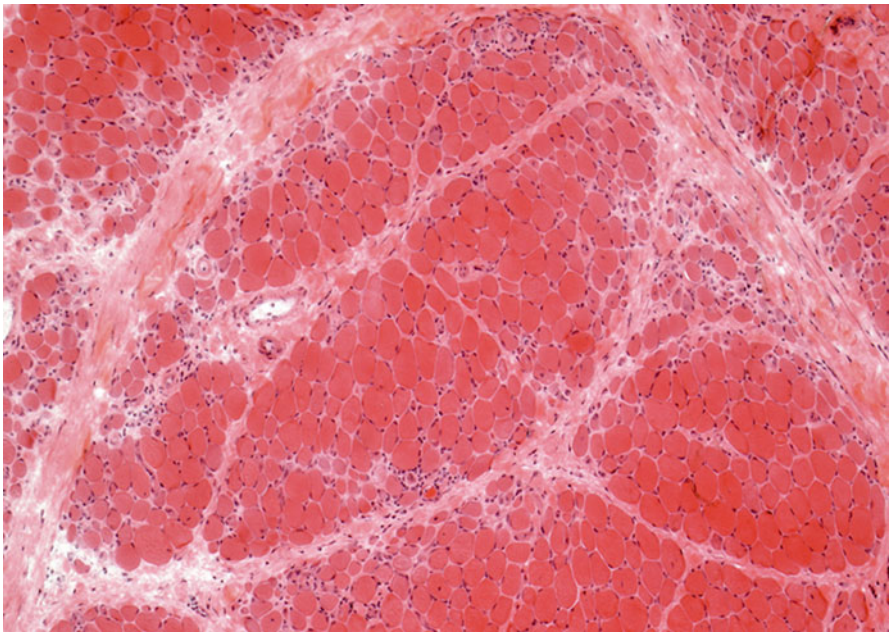

Fig. 6.1 Cross section of a muscle biopsy demonstrates the classic for DM perifascicular atrophy (layers of atrophic fibers at the periphery of the fascicle) with some inflammatory infiltrates

or the periphery of the fascicles along with phagocytosis, and muscle-fiber necrosis prominently at the periphery of the fascicles due to microinfarcts that eventually lead to muscle ischemia, hypoperfusion, and perifascicular atrophy [1–4, 6]. Perifascicular atrophy, characterized by layers of atrophic fibers at the periphery of the fascicles, is diagnostic of DM [1–4, 6] (Fig. 6.1). In PM and IBM, the inflammation is in multiple foci within the endomysial parenchyma and consists predominantly of CD8+ cells invading healthy, nonnecrotic, muscle fibers expressing the MHC-I antigen (Fig. 6.2). The MHC/DC8 complex is useful to confirm the diagnosis and exclude disorders with nonimmune inflammation, as seen in some muscular dystrophies [2–4]. In IBM, in addition to the inflammatory features and the CD8/MHC complex, there are also chronic myopathic changes with increased connective tissue and fiber-size variability, autophagic vacuoles with bluish-red material (Fig. 6.3), "ragged-red" or cytochrome oxidase-negative fibers due to abnormal mitochondria, and congophilic amyloid deposits next to the vacuoles best visualized with crystal violet or fluorescent optics [1–4, 11–14]. By electron microscopy, 12–16 nμ tubulofilamentous inclusions in the vicinity of the vacuoles are recognized [11]. In about 15–20 % of patients with typical clinical IBM phenotype, the biopsies do not show vacuoles or convincing amyloid deposits but only inflammation, leading to erroneous diagnosis of PM [2, 15]. Such patients have "clinical IBM" a concept that emphasizes the need to diagnose IBM based on clinicopathologic correlations, beyond the microscope [2, 15, 16]; the combination of

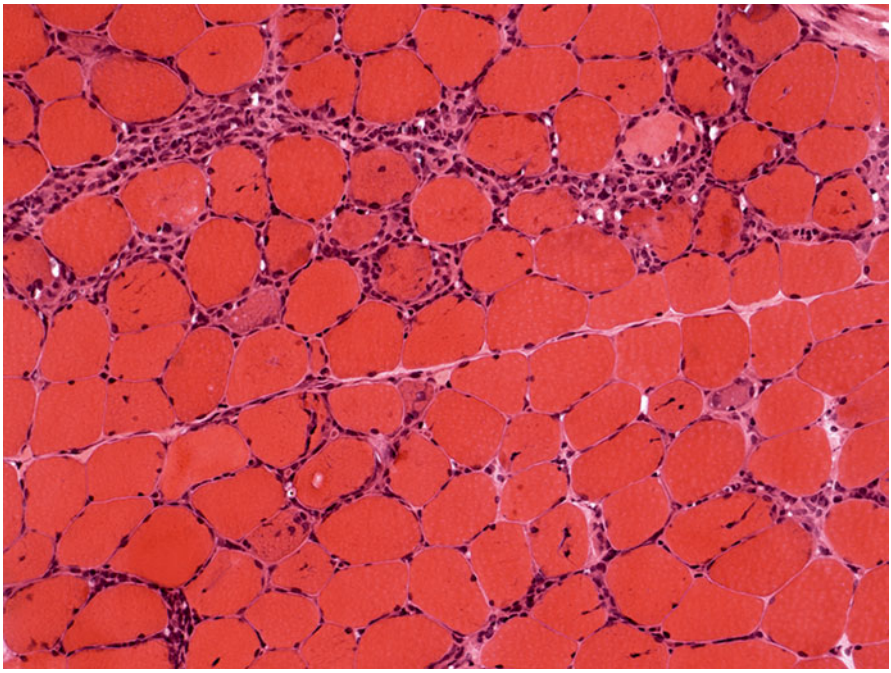

Fig. 6.2 Cross section of a muscle biopsy from a patient with polymyositis demonstrates scattered inflammatory foci with lymphocytes invading or surrounding healthy-appearing muscle fibers

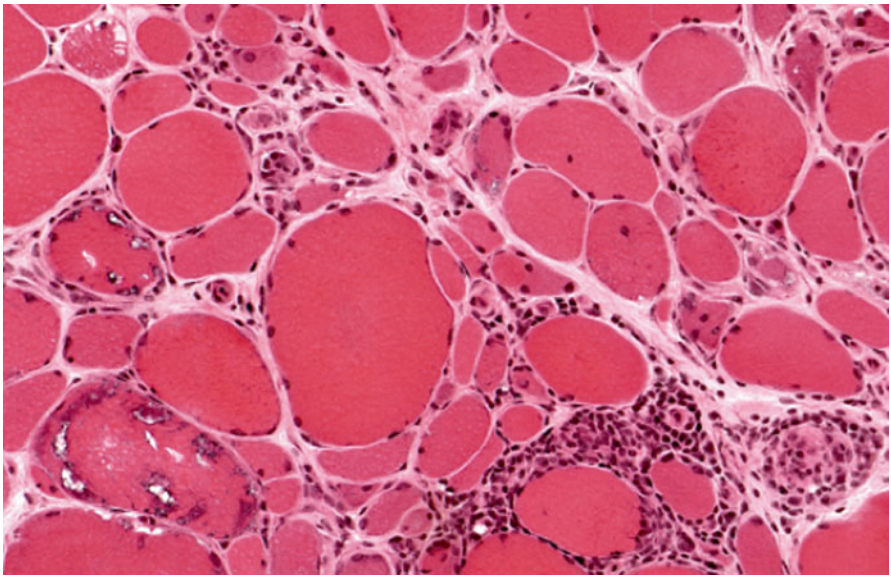

Fig. 6.3 Cross section of a muscle biopsy from a patient with IBM demonstrates inflammatory infiltrates invading or surrounding healthy muscle fibers along with chronic myopathic features based on increased connective tissue, atrophic and hypertrophic fibers, and the typical autophagic vacuoles with bluish-red material, in areas noninvaded by T cells

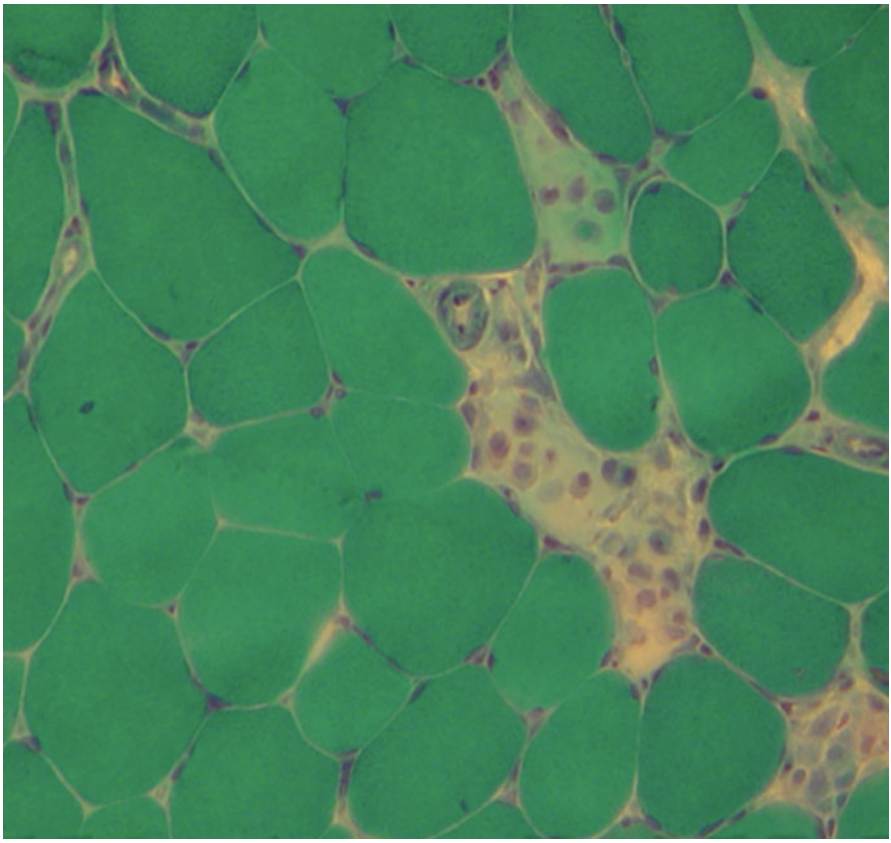

Fig. 6.4 Section of muscle biopsy from a patient within NAM shows scattered necrotic fibers invaded by macrophages

selective finger flexor or quadriceps weakness, endomysial inflammation with MHC-I expression, and cytochrome-oxidase-negative fibers is diagnostic of IBM even if vacuoles or congophilic deposits are absent [2, 15–17]. In NAM there are abundant necrotic fibers invaded or surrounded by macrophages (Fig. 6.4). There are no lymphocytic infiltrates or vacuoles, but MHC-I is upregulated in some areas, even beyond the necrotic fibers [2]

6.7.5 Autoantibodies

Autoantibodies, directed against nuclear or cytoplasmic antigens, are found in as many as 65–70 % of IM patients depending on the series and methodology used [2, 8–10, 18]. Among those, the most specific or useful for diagnosis are the antibodies against ribonucleoproteins involved in protein synthesis (antisynthetases) or translational transport (anti-signal-recognition particles (SRP)). The antibody against histidyl-transfer RNA synthetase, called *anti-Jo-1*, accounts for 75 % of all antisynthetases and is useful because it identifies patients with interstitial lung disease

especially those with overlap myositis [2, 8]. In NAM, two antibodies are diagnostic: one against HMGCR, the pharmacological target of statins, found more often in statin-naive NAM patients, [2, 9, 10, 18–20] and another against SRP [2, 8, 18]. Antibodies against cytosolic 5′-nucleotidase 1A are detected in about 50 % of IBM patients [21, 22]; their presence simply highlights B-cell activation but they lack specificity as they are also seen in other conditions. Other autoantibodies, proposed as markers of malignancy-associated DM, such as melanoma differentiation-associated protein-5 (MDA-5) and nuclear matrix protein NXP-2 [2, 8–10, 18, 23], have not yet shown the sensitivity and specificity needed for routine use.

6.8 Pathogenesis

Although the factors triggering IM are unknown, autoimmune mechanisms – different for each subtype – are strongly implicated.

6.8.1 Dermatomyositis

In DM, there is early activation of complement C5b-9 membranolytic attack complex (MAC) which is deposited on the endothelial cells, leading to necrosis, reduction of endomysial capillaries, ischemia, and muscle-fiber destruction [1–6, 24, 25]; the remaining capillaries have dilated lumen to compensate for the ischemia [2] (Fig. 6.5). The residual perifascicular atrophy reflects the endofascicular hypoperfusion, which is most prominent at the periphery of the fascicles [1–4, 6]. The MAC activation triggers the release of proinflammatory cytokines, induces expression of adhesion molecules on endothelial cells, and facilitates migration of activated lymphoid cells to perimysial and endomysial spaces. The inflammatory infiltrates consist of B cells, CD4+ cells, and plasmacytoid-dendritic cells [2]. Innate immunity also plays a role based on increased expression of type I interferon-inducible proteins in the perifascicular regions [26]; this effect may have a role in enhancing local inflammation after the primary complement-mediated ischemic damage has taken place [27] (Fig. 6.5).

6.8.2 Polymyositis and IBM

In PM and IBM, CD8+ cytotoxic cells surround and invade healthy, nonnecrotic muscle fibers that aberrantly express MHC-I (Fig. 6.6) [1–4, 6, 28–32]. MHC-I expression, absent from the sarcolemma of normal muscle fibers, is probably induced by cytokines secreted by activated T cells [1–4, 6]. The CD8/MHC-I complex is characteristic for PM and IBM [2, 29–33] and its detection aids in confirming the histologic diagnosis [2, 3, 32, 33]. The CD8 cells contain perforin and granzyme granules directed toward the surface of the muscle fibers resulting in myonecrosis upon release [2, 34]. Analysis of T-cell receptor molecules expressed by the infiltrating CD8+ cells reveals clonal expansion and conserved sequences in

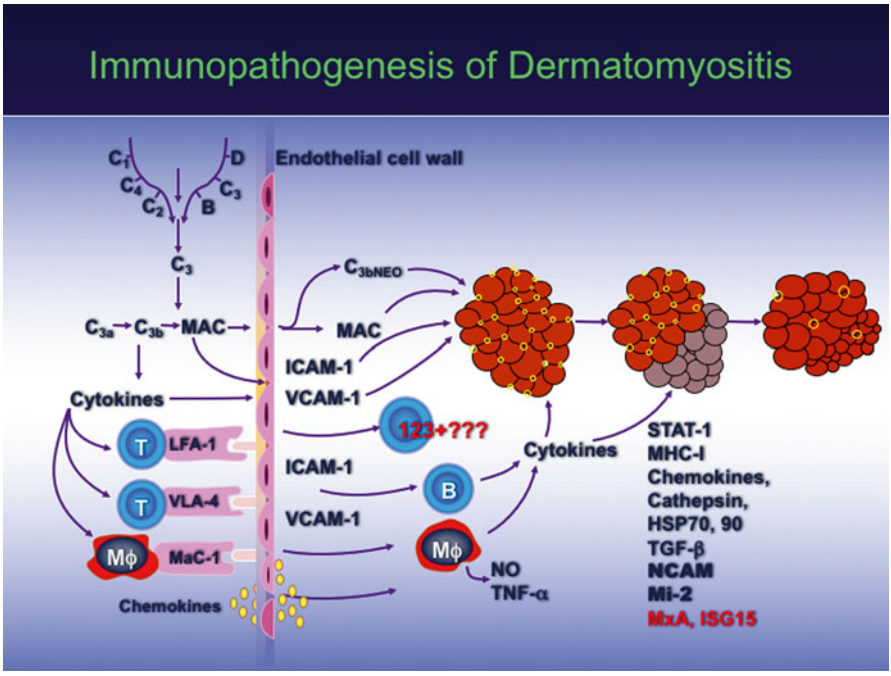

Fig. 6.5 Proposed immunopathogenic scheme of dermatomyositis. Activation of complement C3 is an early event leading to formation of C3b, C3bNEO, and membrane attack complexes (MAC), which are deposited on the endothelial cell wall of the endomysial capillaries, resulting in destruction of capillaries, ischemia, or microinfarcts, most prominent in the periphery of the fascicles, and perifascicular atrophy. Cytokines released by activated complement lead to activation of CD4+ T cells, macrophages, B cells, and 123+ plasmacytoid-dendritic cells (PDC); enhance the expression of vascular cell adhesion molecules (VCAM) and intercellular adhesion molecule (ICAM) on the endothelial cell wall; and facilitate lymphoid cell transmigration to endomysial tissue by their integrins, late activation antigen (VLA)-4, and lymphocyte function-associated antigen (LFA)-1 which bind VCAM and ICAM. The perifascicular regions contain fibers in a state of remodeling and regeneration (expressing TGFβ, NCAM, Mi-2), cell stress (expressing HSP 70, 90), immune activation (expressing MHC-1, chemokines, STAT-1), and molecules associated with innate immunity (such as MxA, ISG15, Rig-1). The role of innate immunity in inflammation and perifascicular atrophy appears secondary to hypoxic and ischemic damage sensed by the retinoic acid-inducible gene-1 (Rig-1) signaling, which in turn leads to auto-amplification of the local inflammation via β-interferon [27]

the antigen-binding region, suggesting an antigen-driven T-cell response [34–39]. This is further supported by the rearrangement of the T-cell receptor genes, the expression of co-stimulatory molecules and their counterreceptors, and the upregulation of adhesion molecules and cytokines [2–4, 35–42] (Fig. 6.6). There is also B-cell activation, most prominent in IBM [43], as supported by B-cell and plasma cell infiltrates and the presence of autoantibodies against nuclear antigens, initially reported 15 years ago [44], and recently identified as being against 5′-nucleotidase 1A [21, 22].

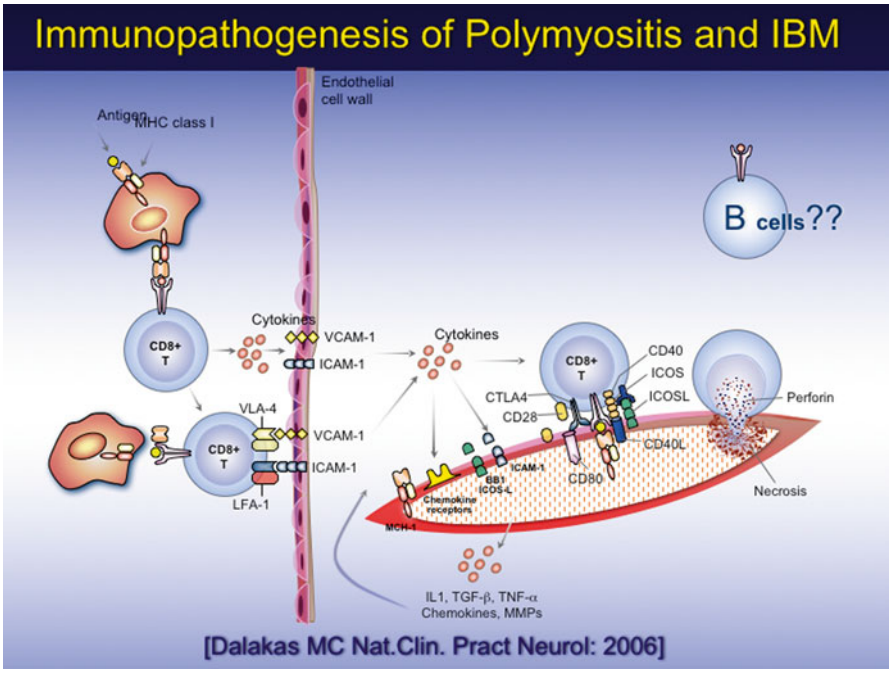

Fig. 6.6 Proposed mechanism of T-cell-mediated muscle damage in polymyositis (PM) and inclusion-body myositis (IBM). Antigen-specific CD8+ cells, expanded in the periphery and subsequently endomysially, cross the endothelial cell wall and bind directly to aberrantly expressed MHC-I on the surface of muscle fibers via their T-cell receptors. Upregulation of co-stimulatory molecules (BB1 and ICOSL) and their ligands (CD28, CTLA-4, and ICOS), along with ICAM-1/LFA-1, stabilizes the synaptic interaction between CD8+ cells and MHC-1 on muscle fibers. Perforin granules released by the autoaggressive T cells mediate muscle-fiber necrosis. Cytokines, such as interferon (IFN-γ), interleukins (IL- 1), and tumor necrosis factor (TNF-α) released by the activated T cells, may enhance MHC-I upregulation and T-cell cytotoxicity. Activated B cells or plasmacytoid-dendritic cells are clonally expanded endomysially and may participate in the process by a still undefined role, either as antigen-presenting cells (APC) or by release of cytokines and antibody production

What triggers disease remains unknown. Genetic risk factors regulating immune responses against undefined environmental agents have been proposed [8]. Viruses may be responsible for breaking tolerance but attempts to amplify viruses from these muscles, including coxsackieviruses, influenza, paramyxoviruses, mumps, cytomegalovirus, and Epstein-Barr, have failed [2–4, 6]. The best evidence for a viral connection is with retroviruses because individuals infected with HIV or human T-cell lymphotropic virus-I develop typical PM or IBM [45–47]; PM is also seen in primates infected with simian immunodeficiency virus [2, 45]. Retroviral antigens are only detected in endomysial macrophages but not within the muscle fibers themselves. The autoinvasive T cells are clonally driven and some retroviral specific [45]. HIV-PM and HIV-IBM should be distinguished from a toxic mitochondrial myopathy, induced by antiretrovirals, which improves upon drug discontinuation [48].

The complexity of IBM: *the role of nonimmune factors and "cross talk" between inflammation and degeneration.* In IBM, in addition to autoimmunity, there is an important neurodegenerative component, evident by the presence of congophilic amyloid deposits within some fibers [2, 3, 11–13, 49]. Similar to Alzheimer's disease, these deposits immunoreact against amyloid precursor protein (APP), amyloid β-42, apolipoprotein E, α-synuclein, presenilin, ubiquitin, and phosphorylated-tau attesting to protein aggregation [2, 11, 49]. Immunostaining for the ubiquitin or tau components, TDP43 and p62, has been advocated as diagnostic markers [11, 49, 50]. There is in vitro evidence that β-amyloid is involved in the pathway of intracellular toxicity [49] but remains unclear how these proteinaceous aggregates, which are also seen in other vacuolar myopathies, induce an inflammatory vacuolar myopathy and what triggers disease, inflammation, or protein aggregation [2]. Aging, abnormal proteostasis (the network controlling proteins) [49], cell stress induced by MHC-1 or nitric oxide [51, 52], and long-standing inflammation with proinflammatory cytokines, such as interferon-γ and IL1-β [51–54], may cumulatively play a role either in triggering the disease process or enhancing degeneration and further accumulation of stressor molecules and misfolded proteins [2, 53].

6.9 Treatment of DM, PM, and NAM

Oral prednisone is the first-line drug based on experience, but not controlled trials [1–4, 55, 56]. In patients with severe or rapidly worsening disease, intravenous methylprednisolone for 3–5 days is preferable before starting the oral regimen. After 3–4 weeks, the daily dose is switched to alternate days [2, 54–56]. If by the 3rd month there are no objective signs of increased strength and activities in daily living, tapering should be accelerated to start the next in-line agent. A tactical error is the practice of "chasing" the CK level as a sign of response, especially in patients reporting a sense of "feeling better" but not necessarily stronger. When the strength improves, the serum CK drops, but fall in CK alone, should not be interpreted as a sign of improvement [2–5, 33]. In steroid-responsive patients, the drugs most commonly used for "steroid-sparing" are empirical and include *azathioprine*, *mycophenolate mofetil*, *methotrexate*, or *cyclosporine* [1–4, 54, 55]. *Cyclophosphamide* or *tacrolimus* may be helpful when interstitial lung disease coexists [1–4, 57]. When corticosteroids fail to induce remission, or in rapidly progressive cases, *intravenous immunoglobulin* (IVIg) at 2 g/kg is the most appropriate next in-line drug [2, 55, 56, 58, 59]. In a double-blind study, IVIg was effective in refractory dermatomyositis [58]. The improvement is noticeable after 15 days, but monthly infusions are required to maintain remission. In open-label trials, IVIg is also effective in several PM and NAM patients [2, 55]. Subcutaneous Ig, a possibly more practical or cost-effective means of infusing IgG, has shown promise in sustaining remission [60].

If corticosteroids and IVIg have failed to improve strength, it is prudent to reevaluate the patient, challenge the diagnosis, or reconsider a repeat muscle biopsy. If the diagnosis is reconfirmed, new biologics approved for other autoimmune diseases may be considered, as discussed [2, 55]. Among those the most promising is

rituximab, which at 2 g (divided in 2 biweekly infusions) can be effective in several DM, PM, and NAM patients [61–63]. A placebo-controlled study in 200 patients however did not meet the primary end point largely because of study design [64]. Although at week 8 there was no difference between placebo and rituximab, at week 44 when all patients had received rituximab, 83 % met the definition of improvement [64]. Patients with autoantibodies against Jo-1, Mi-2, or SRP were more likely to improve [65]. Anti-*TNF-α inhibitors* (infliximab, adalimumab, etanercept) anecdotally used [66] have been ineffective and may even worsen or trigger disease [67]. Other biologics for future experimental trials may include *alemtuzumab*, reportedly effective in PM [68]; *anti-complement C3* (*eculizumab*), effective in other complement-mediated diseases, might be appropriate for DM and NAM [2] and new agents against immunoregulatory cytokines, such as *anti-IL-6*, *anti-IL17*, *or IL17A* [2, 55]. All these trials have been small and better-designed studies with more adequate power are needed. Overall, the long-term outcome of IM has substantially improved, with a 10-year survival rate in one recent study to be at >90 % [69, 70].

6.10 Treatment of IBM

Because a T-cell-mediated cytotoxicity coexists with degeneration and proinflammatory cytokines enhance amyloid aggregates [2, 51–54], strong anti-inflammatory agents should theoretically halt disease progression. All such agents however have failed probably because IBM starts long before patients seek medical advice, when the degenerative cascade is already advanced [2, 54]. Corticosteroids, methotrexate, cyclosporine, azathioprine, and mycophenolate are ineffective, although some patients may initially respond to some degree [2, 54]. IVIg is ineffective in controlled trials but may transiently help some patients, especially the dysphagia [1–73]. Alemtuzumab may provide short-term stabilization [74] but a controlled study is needed. Anti-ILI receptor (Anakinra) failed [75]. Trials targeting muscle-inhibiting TGF-b molecules or muscle growth factors are in progress.

At present, symptomatic therapies are the best options. For life-threatening dysphagia not responding to IVIg, cricopharyngeal myotomy may be considered [76]. Because of coexisting mitochondrial dysfunction, co-enzyme Q_{10} may enhance endurance, although never properly tested. Non-fatiguing, resistance exercises can be beneficial [77]. Like in all IM, occupational and rehabilitation therapies are useful to improve ambulation, prevent falling, avoid disuse atrophy, and prevent joint contractures.

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Necrotizing Autoimmune Myopathy

7

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7.1 Introduction

Necrotizing autoimmune myopathy (NAM) is an idiopathic immune-mediated myopathy, along with dermatomyositis (DM), polymyositis (PM), and sporadic inclusion body myositis (sIBM). NAM manifests with subacute proximal-predominant muscle weakness and elevated serum creatine kinase (CK). Pathologically it is characterized by prominent muscle fiber necrosis and regeneration, but, contrary to the other idiopathic immune-mediated myopathies, it is accompanied by minimal or no inflammation [1–3]. For this reason, although in the literature NAM or other immune-mediated myopathies are sometimes referred to as "idiopathic inflammatory myopathies" (IIM), we prefer to avoid the term IIM.

The literature around NAM has expanded in recent years with the discovery of serum antibodies associated with this disease, including antibodies to signal recognition particle (SRP) and 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR). As will be discussed in this chapter, the presumed immune basis of NAM rests on the subacute onset, clinical response to immunotherapy, and associated serum antibody profile. The etiology of NAM is unknown, but the disease can occur in isolation, in association with statins, connective tissue diseases, or malignancy. Similar to other rare diseases, the epidemiology, risk factors, and response to treatment remain incompletely understood.

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7.2 Clinical Features and Epidemiology

Most patients with NAM present during adulthood between the second and the sixth decade, but the disease can also manifest in the elderly and childhood. Overall, there seems to be no clear male or female predominance, and different studies have shown conflicting results in this regard. The typical clinical presentation of NAM is of relatively symmetric proximally predominant weakness that progresses subacutely (over days, weeks, or a few months) in most cases [4–7]. NAM often manifests in a more fulminant manner than typically seen in inflammatory myopathies, and more than 50 % of patients develop severe weakness. However, some reported NAM cases have presented insidiously over many months, mimicking muscular dystrophy and making the diagnosis challenging [8].

Lower limb weakness tends to be more severe than upper limb weakness, and patients often complain of difficulties arising from a chair, climbing stairs, or ambulating [4]. Distal weakness is common, although less severe than proximal weakness. We observed distal weakness in 41 % of our patients, mainly affecting wrist and finger extensors and/or foot dorsiflexors [4]. Axial weakness occurs in 30–80 % of patients and neck flexor are more commonly involved than neck extensor muscles. Occasionally, neck muscle weakness can be the predominant clinical feature [4]. Bulbar muscles may be affected with one-third of patients experiencing dysphagia, whereas dysarthria is uncommon (only 6 % in one series) [4]. Myalgias occur in approximately one-third of the patients. Table 7.1 lists many of the clinical features and frequencies for our large cohort of NAM patients [4].

In their early report of SRP antibody-associated necrotizing myopathy, Pestronk and colleagues noted a predilection for symptoms to start in the fall, but several subsequent reports did not confirm this observation. Antecedent events that could potentially trigger a dysimmune response and NAM are rare, with upper respiratory tract illnesses and surgical procedures noted within 2 weeks prior to weakness onset in few cases [4]. However, the role of these events in the pathogenesis of NAM is unknown.

Table 7.1 Clinical features and frequencies in 63 NAM patients evaluated at Mayo Clinic

Clinical feature	Frequency (%)
Proximal muscle weakness	100
Distal muscle weakness	41
Neck flexor weakness	78
Neck extensor weakness	31
Facial muscle weakness	14
Dysphagia	35
Dysarthria	6
Dyspnea	37
Myalgia	35
Weight loss	29

Rash is extremely rare in NAM. The characteristic skin manifestations of DM are not observed. However, if a patient has a coexisting connective tissue disease, the dermatological or systemic features of the specific connective tissue disease (e.g., scleroderma) can be observed. Raynaud phenomenon can occur. Weight loss around the time of presentation of NAM is not uncommon and observed in about 30 % of cases [4].

7.3 Pulmonary and Cardiac Manifestations

The frequency of cardiac or respiratory involvement in NAM varies greatly in the literature, likely a reflection of inconsistent assessment and definition of restrictive lung disease, interstitial lung disease (ILD), and critical consideration of comorbidities. Many patients with NAM may have risk factors for coronary artery disease or cardiomyopathy, which may account for any detected arrhythmias or cardiac conduction defects seen on electrocardiogram. Nevertheless, respiratory muscle involvement and cardiac manifestations occur in NAM.

In our series, 37 % of patients complained of dyspnea and 5 of 63 had hypercapnic respiratory failure requiring mechanical ventilation [4]. In addition, among patients who underwent complete pulmonary function testing, approximately a third had a restrictive pattern suggestive of respiratory muscle weakness [4]. Data on the frequency of ILD in NAM are conflicting. In some series, ILD was very rare in NAM [4, 9] (only 2 of 63 patients had findings consistent with ILD in our cohort [4]), whereas there was a higher incidence of ILD in NAM patients with SRP antibodies (21 % of SRP-IgG-associated NAM in one series [10]). There may be a higher incidence of ILD in patients with immune-mediated myopathies associated with connective tissue disease, especially in systemic sclerosis [11].

Cardiac involvement is less common than pulmonary impairment. Patients can have palpitations and chest pain. Similarly to other immune-mediated myopathies, the cardiac conduction system appears preferentially involved in NAM, since arrhythmias and conduction defects, such as bundle branch blocks and prolonged QTc interval, are more commonly observed than structural cardiomyopathy [12].

7.4 Risk Factors and Etiologies

Although several risk factors or disease associations have been reported in NAM, the majority of NAM patients are “idiopathic” [4]. One of the earliest identified associations was of cancer (paraneoplastic necrotizing myopathy), described in several case reports and case series [13, 14]. The cancers reported in association with NAM include non-small cell lung cancer, bladder (transitional cell), gastric, colon, prostate, and pancreatic adenocarcinomas. In our series of 63 NAM cases, six were paraneoplastic, with gastrointestinal tumors being most common (two colon adenocarcinomas, one esophageal adenocarcinoma), followed by one case each of lung adenocarcinoma, ovarian adenocarcinoma, and thymoma [4]. Other authors have detected cancer in association with NAM, including anti-HMGCR antibody-positive

NAM cases [15]. In many cases, the underlying cancer is discovered after the onset of the myopathy, during the malignancy screen prompted by the diagnosis of NAM. These data suggest that patients with NAM should be screened for an underlying malignancy by physical examination (prostate, breast), imaging studies (chest, abdomen, pelvis, breast), and gastrointestinal tract endoscopy. However, one should also be aware that no increased risk of cancer was detected in another large series of NAM cases in comparison with the general population [7].

Rarely, NAM has been associated with connective tissue diseases, including systemic lupus erythematosus [7], scleroderma [4], Sjogren syndrome [4], or an undifferentiated connective tissue disease [16]. In these cases, patients often have multisystemic symptoms or clinical signs suggestive of the underlying connective tissue disease and a compatible serological autoantibody profile. There is no convincing evidence that NAM patients with an underlying connective tissue disease have a different clinical course than other NAM patients, but the small numbers of reported cases preclude reliable conclusions.

Statins appear to be the most common risk factor association in patients with NAM. Several studies have demonstrated an increased risk of myopathy, including NAM, in patients taking statin medications [17–19]. In patients exposed to statins, who develop myopathic symptoms and elevated serum CK, NAM should be suspected if there is no clinical or serological improvement after discontinuation of the statin. Patients may be on statins for months or years (2 months to 10 years in one study) before developing NAM, and in some cases NAM has occurred many months after statin discontinuation [17]. In these cases, it may be difficult to identify the statin as the underlying trigger.

Recently, an antibody directed against HMGCR (the enzyme inhibited by statin medications) has been identified in some NAM patients [19, 20]. Interestingly, not all statin-exposed NAM patients have HMGCR-IgG antibodies, and conversely not all HMGCR-IgG-positive patients have a history of statin exposure [4, 18, 19]. Thus, the exact pathogenesis and role of HMGCR antibodies in NAM remains unknown (see section below on autoantibodies in NAM).

Interestingly, regardless of disease or drug association (paraneoplastic, connective tissue disease, or statin), there appear to be no significant differences in clinical severity, extra-muscular manifestations, serum CK, or clinical outcome [4]. Statin-associated NAM patients tend to be older and are more likely to have myotonic discharges on EMG, whereas idiopathic cases are more likely to have dysphagia.

7.5 Diagnostic Workup and Laboratory Testing

7.5.1 Antibodies in NAM

Several autoantibodies have been recognized to occur in NAM, with the most well-characterized being SRP-IgG and HMGCR-IgG antibodies.

SRP-IgG is most commonly associated with NAM but has been rarely reported in other immune-mediated myopathies, such as DM and sIBM [10, 21, 22]. In a

study on antibody profiles of myositis patients (PM, DM, and IBM), approximately 5 % of cases were SRP-IgG positive [21]. Characteristically, patients with SRP-IgG-related NAM have relatively rapid onset of severe weakness (significant disability within 6 months) that is often refractory to commonly used immunotherapy (e.g., monotherapy with oral prednisone) [5, 10]. Some investigators believe that SRP-IgG-positive NAM is more resistant to treatment than non-SRP antibody-positive NAM. Although patients with SRP-IgG-associated NAM rarely have an underlying malignancy, the presence of SRP-IgG does not exclude an associated cancer [10, 23].

Antibodies targeting HMGCR have recently been discovered in the sera of NAM patients [19, 20]. Similar to other NAM patients, HMGCR-IgG-positive cases demonstrate severe proximal weakness and markedly elevated serum CK, associated with axial weakness and dysphagia in many cases. A restrictive pattern of respiratory weakness occurs in up to 25 % of cases, while cardiac conduction defects have been rarely reported in HMGCR-IgG-positive NAM [18]. Interestingly, statin drug exposure is not required for the development of HMGCR-IgG-associated NAM, and 20–70 % of HMGCR-IgG-positive NAM cases are statin naïve [4, 18, 19, 24]. Phenotypic differences are present between HMGCR-IgG-positive patients exposed to statin and those not exposed to it. HMGCR-IgG-positive NAM patients with a history of statin medication exposure tend to be older, are less likely to be African American, and may be more responsive to immunotherapy [24]. In regard to statin-naïve NAM patients, one should consider that these patients may be exposed to statins contained in aliments (e.g., oyster mushrooms contain lovastatin), and therefore they may not be truly statin naive. Underlying malignancies have also been reported in HMGCR-IgG-positive NAM, with the malignancy usually discovered after the onset of myopathy [15, 18]. Thus far, only a single patient has been reported to be dual positive for SRP-IgG and HMGCR-IgG [4].

Other autoantibodies that have been reported in NAM patients include PL-12 [25], PL-7 [20], Ku [7, 26], and Jo-1 [4, 20].

7.5.2 Serum CK

The serum CK is usually markedly elevated in most NAM cases, but ranging from 600 to 30,000 IU/L. When following patients clinically over time, rises and declines in serum CK level occur with clinical relapse or improvement, respectively. So, the serum CK may be used in conjunction with clinical weakness as a surrogate marker of overall disease activity when following patients [6].

7.5.3 Electromyography (EMG)

Nerve conduction studies (NCS) and needle EMG are useful tests to confirm a myopathic process and rule out other neuromuscular causes of weakness. Needle EMG demonstrates fibrillation potentials and short-duration, low-amplitude (myopathic)

motor unit potentials in clinically weak muscles [1, 2, 4, 5]. Myotonic discharges may be recorded and are significantly more common in patients with statin-associated NAM [4]. Although prospective studies are lacking, our 11 patients who underwent posttreatment follow-up EMG studies showed a reduction in the number of muscles with fibrillation potentials and myopathic motor unit potentials [4].

7.5.4 Muscle Imaging

Magnetic resonance imaging (MRI), the preferred method of imaging muscle, can provide useful information but often is not necessary for patient care. Increased signal on short tau inversion recovery (STIR) sequences suggests muscle degeneration and necrosis, although does not indicate its etiology. MRI has the potential to improve the diagnostic yield of a muscle biopsy by allowing the clinician to target a weak muscle that is abnormal but not end-stage and completely replaced by fatty connective tissue [27].

7.5.5 Muscle Biopsy

A muscle biopsy is critical to confirm the diagnosis of NAM raised by the clinical history, while excluding other myopathies. The histopathological hallmark of NAM is the presence of necrotic and regenerating muscle fibers, with minimal or no inflammatory infiltrate (Fig. 7.1) [1, 2]. In many biopsies, necrotic muscle fibers are invaded by CD-68-positive macrophages, which may give the false impression of an inflammatory exudate. Nevertheless, approximately 20 % of NAM biopsies show some degree of inflammatory infiltrate [4]. This usually consists of small collections of mononuclear cells located at perivascular sites in the perimysium or in proximity to necrotic muscle fibers. The autoaggressive inflammatory exudate with mononuclear cells invading non-necrotic muscle fibers, typical of PM and sIBM, does not occur in NAM. Likewise, the perifascicular preference of the structural abnormalities, classically observed in DM, is not present in NAM. Thickening of the capillary basement membranes ("pipestem capillaries") and capillary depletion has been rarely reported in NAM [5, 16]. Non-rimmed vacuoles can be observed [4]. Often the pathological features of NAM are those of a nonspecific myopathic process and alone cannot confirm the diagnosis of NAM, which should be supported by the clinical history and serological data. For this reason, if clinically indicated, immunohistochemical studies to localize sarcolemmal, cytosolic, or nuclear proteins responsible of muscular dystrophies may be warranted to try to exclude inherited myopathies.

In SRP-IgG-positive muscle biopsies, some authors found a reduced capillary density compared to controls, and membrane attack complex (MAC) deposition in most endomysial capillaries but not diffusely on muscle fibers [5]. However, these findings were not confirmed by others [10].

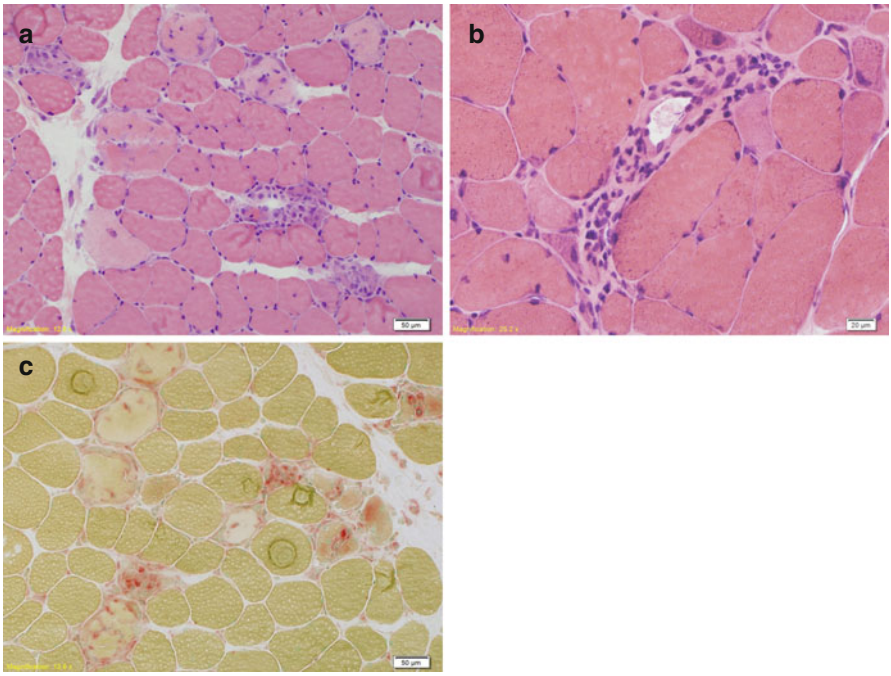

Fig. 7.1 Muscle biopsy of patients with HMGCR-IgG antibody-positive necrotizing autoimmune myopathy. Hematoxylin-eosin stained section shows scattered necrotic and fewer regenerating muscle fibers (**a**) and rare inflammatory cells a perivascular site in the perimysium of another NAM patient (**b**). Some necrotic fibers have been invaded by macrophages, which stain red in acid phosphatase-reacted section (**c**) (**a**, **c**: magnification 20×; **b**: magnification 40×)

In HMGCR-IgG-positive NAM muscle biopsies, several authors have reported upregulation of the major histocompatibility complex class I antigen (MHC-1) [15, 28], while there are discrepant results about the presence of complement deposition on the sarcolemma of non-necrotic muscle fibers and endothelial cells [15, 28]. Some authors have also described enlargement and irregular shape of the myonuclei [15]. The pathological changes seem independent of statin exposure. Characterization of the limited inflammatory exudate in muscle biopsies of HMGCR-IgG-positive NAM patients identified CD-68-positive cells (macrophages) as the most common mononuclear cell type in both endomysium and perimysium [28]. Scattered CD-4- and CD-8-positive T-cells were also noted in the endomysium and perivascular sites; CD-20-positive cells were rare. Plasmacytoid dendritic cells (CD-123 positive) were found in 63 % of biopsies, suggesting a role for innate immunity and interferons in the disease pathogenesis. Based on these results, the authors hypothesize that HMGCR antibodies may bind to the cell surface and activate complement to initiate muscle fiber lysis [28].

7.6 Diagnosis and Differential Diagnosis

There is no gold standard diagnostic test for NAM. Clinical history plays a critical role in the diagnosis, and results of serological, EMG, and muscle pathological studies all contribute to the correct diagnosis. Response to immunotherapy corroborates it [1, 2].

Basic blood tests are useful for excluding alternate diagnoses as causes of proximal weakness and elevated serum CK, as well as other forms of necrotizing myopathy, such as necrotizing myopathy associated with HIV infection [29], hypothyroidism [30], or drug toxicity [31].

The EMG helps to confirm that the weakness has a myopathic basis, and the presence of myotonic discharges (more common in statin-associated NAM) may be a clue to the etiology.

The muscle biopsy is critical to confirm that the predominant pathological features are muscle fiber necrosis and regeneration and to exclude inflammatory immune-mediated myopathies. The biopsy is also helpful in excluding hereditary myopathies with specific structural abnormalities or reduced protein expression.

There is an increasing tendency to use serum antibody profile to diagnose NAM, particularly with the recent identification of HMGCR-IgG. Although HMGCR-IgG and SRP-IgG are valuable in supporting the autoimmune etiology of a necrotizing myopathy, they do not have a very high sensitivity, and their absence does not exclude the diagnosis of NAM [7, 21, 26, 32]. Additionally, SRP-IgG is not very specific and has been reported in other inflammatory myopathies and in patients without myositis [10, 33].

In light of the data linking NAM to various malignancies, a malignancy screen is recommended for all NAM patients. This could include imaging of the chest, abdomen, and pelvis, mammogram, as well as esophagogastroduodenoscopy and colonoscopy.

7.7 Pathophysiology

The pathogenesis of NAM is not fully understood. The identification of autoantibodies in many patients, such as SRP-IgG and HMGCR-IgG, may suggest an antibody-mediated mechanism, with complement activation leading to cell lysis and fiber necrosis. However, the pathogenicity of the antibodies remains undefined and the subject of active investigation.

SRP is a family of proteins that participate in the protein synthetic pathway, assisting in the docking of newly formed proteins to the endoplasmic reticulum. In one study, in vitro human myoblast cultures incubated with serum from patients with SRP-IgG-positive NAM and complement demonstrated lower survival, and aberrant expression of SRP on the sarcolemmal surface [34]. The authors hypothesize that patients with circulating SRP-IgG antibodies may have abnormal surface

expression of SRP that results in antigen-antibody complex formation and activation of complement-mediated cell lysis and necrosis.

The pathogenic role of statins and of the HMGCR-IgG antibodies also remains unclear. HMGCR-IgG is thought to be highly specific for NAM, rather than for a self-limited statin-associated myopathy that resolves with discontinuation of the drug [35], although rare self-limited HMGCR-IgG-positive cases have been reported [18].

The correlation between the HMGCR-IgG titer drop and the improved muscle strength in statin-exposed patients provides indirect evidence of the possible pathogenicity of these antibodies [18, 24]. Similarly, the serum SRP-IgG titer was found to correlate with the serum CK, and both declined with treatment and clinical improvement [6].

In cases of statin-associated NAM, there is likely an interplay between a agenetic predisposition and the environmental trigger (the statin medication). Support for this hypothesis comes from a study showing that the DRB1*11:01 haplotype was more common in patients with HMGCR-IgG-associated NAM compared to normal controls [36]. This haplotype may thus confer an enhanced ability of the antigen-presenting cell to activate an immune reaction in response to statin exposure.

The lack of prominent T-cell infiltrates in NAM points away from the cytotoxic T-cell-mediated mechanism invoked PM and sIBM. The MHC-1 upregulation is not very helpful in defining disease mechanism because it can also occur in hereditary myopathies.

7.8 Treatment and Prognosis

There are no prospective treatment trials to guide treatment of NAM, and thus recommendations are based on retrospective case series and expert opinion [37]. In general, most experts believe that NAM is more refractory to treatment than PM or DM, requiring more aggressive and prolonged courses of immune therapy [4, 5, 17, 22, 38]. However, there are some data suggesting that many NAM patients may not require more aggressive treatment [39].

In most series, patients were treated initially with corticosteroids (often orally at 1 mg/kg) but required the addition of one or more immunotherapies to control the disease [4, 5, 10, 18, 37, 40]. These additional therapies are most commonly steroid-sparing oral agents (methotrexate, azathioprine, or mycophenolate mofetil) and IVIG. The patient's response to therapy, severity of weakness, and presence of severe complications like respiratory muscle weakness often guides the type of treatment. In our cohort of NAM patients, 56 % required "triple therapy" to control the disease, consisting of corticosteroids (oral or IV), IVIG, and an oral steroid-sparing agent [4, 40], while only 2 of the 63 patients could be treated with corticosteroids alone [4]. Early treatment with IVIG seems to increase the likelihood of strength improvement [4]. In refractory cases, other treatment options have included plasmapheresis, rituximab, cyclosporine, and cyclophosphamide. Several case reports suggest that rituximab in particular may be beneficial in highly refractory patients with SRP-IgG [18, 37, 41, 42].

Thus, based on the available literature, it is reasonable to treat NAM patients with a combination of IVIG, corticosteroids, and a steroid-sparing immunosuppressant for at least 3–4 months, followed by long-term treatment with a steroid-sparing agent. However, in the absence of prospective treatment trials, therapy must be individualized on the basis of disease severity and the response monitored carefully. In cases of paraneoplastic NAM, treatment of the underlying malignancy is necessary; however, these patients usually also require immunotherapy [4, 13, 43].

The risk of clinical relapse with drug tapering or discontinuation is high (over 50 % of cases) [4, 18, 40]. Many studies have shown that patients are rarely able to discontinue all immunotherapy and most require long-term immunosuppression [4, 18]. A study suggested that the greatest improvement in CK values and muscle strength after relapse occurs after reintroduction of high-dose steroids or IVIG [40].

Despite the need for aggressive and long-term immunotherapy, outcomes in NAM can be favorable. In one large cohort of NAM patients, 17 of 32 patients had marked improvement of weakness or returned completely to baseline with aggressive treatment [4]. Some authors found that although many patients had residual weakness, 75 % had normal or near-normal ambulation by the end of their study [10]. Factors that have been identified as possible predictors of favorable outcome include male gender and aggressive treatment with two or more immunosuppressive agents within the first 3 months of presentation [4]. Interestingly, the presence of SRP-IgG or HMGCR-IgG antibodies was not a significant predictor of outcome or treatment response in our study, although some investigators have found that SRP-IgG-positive NAM is more resistant to treatment and may have a poor outcome [44]. There are few data directly comparing treatment efficacy or response rate among NAM cases based on etiology or presence of antibodies, but overall there appear to be few differences [45].

Key Points

- Necrotizing autoimmune myopathy is an immune-mediated muscle disease characterized by subacute, often severe, predominantly proximal muscle weakness and elevated serum CK.
- Dysphagia and respiratory muscle weakness are common and potentially life-threatening complications.
- Muscle biopsies demonstrate predominant necrotic and regenerating muscle fibers, with minimal or absent inflammatory infiltrate.
- NAM may be idiopathic or associated with statin exposure, connective tissue disease, or malignancy.
- Autoantibodies most commonly associated with NAM are SRP-IgG and HMGCR-IgG, although the presence of these antibodies is not required for the diagnosis.
- NAM can be difficult to treat and usually requires aggressive and prolonged immunosuppression, often with IVIG, corticosteroids, and oral steroid-sparing immunosuppressant medications.

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Statin Myopathy

8

Jochen Schaefer and Sandra Jackson

8.1 Epidemiological Impact of Statins in Cardiovascular Disease

Statins inhibit 3-OH-3-methyl-glutaryl-CoA (HMG-CoA) and are the most potent drugs currently available to treat hypercholesterolaemia [1]. These agents form a mainstay of primary and secondary prevention of coronary artery disease and atherosclerosis and effectively reduce cardiovascular mortality [2]. It is estimated that the incidence of heart attacks and strokes is reduced by 20 % for each reduction of 1 mM in LDL cholesterol levels [3]. The average cholesterol-lowering effect of the highest approved statin doses is 33 % for fluvastatin (80 mg) and up to 55 % for atorvastatin (80 mg) [4, 5]. Besides simply reducing plasma cholesterol levels, statins also have pleiotropic (cholesterol-independent) effects, mainly anti-inflammatory and pro-apoptotic, which contribute to the beneficial actions of statins, but also to their side effects [6].

Shortly after their introduction in 1987, the first cases of statin-associated rhabdomyolysis were published in 1988 [7]. Despite this serious adverse event, the risk-benefit ratio remains very much in favour of statin therapy, and indeed statins are now amongst the most widely prescribed drugs worldwide. So far, only one statin, cerivastatin, had to be removed from the market due to an excess of rhabdomyolysis – 50 times greater than other statins [8]. Most deaths, however, had occurred with concomitant administration of other drugs, in particular fibrates and gemfibrozil.

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Table 8.1 Definitions of statin-associated muscle symptoms

Myalgia	Muscle discomfort (soreness, stiffness, tenderness, heaviness, cramps), with normal CK levels. Apparent weakness may occur secondary to pain
Myopathy	Weakness and/or myalgia with elevation of serum CK
Rhabdomyolysis	Myopathy with serum CK >10x ULN plus evidence of associated renal failure or serum CK >10,000 U/l (50-fold elevation)
Asymptomatic myo-pathy	CK elevation without clinical symptoms – this was not defined by the Task Force

8.2 Definition of Statin Myotoxicity

Amongst all side effects of statins, their muscular side effects remain most important and are the crucial factor for patient adherence to statin treatment. In one study [5], the muscle-related side effects were the reason for discontinuation of statin treatment in 65 % of cases.

There is still currently no consensus on the definition of statin myopathy which confuses the interpretation of observational studies of statin-associated muscle symptoms. Moreover, most studies on statin myotoxicity have been performed by non-neuromuscular experts.

In the literature, the most widely accepted definitions are those of the National Lipid Association (NLA) Statin Muscle Safety Task Force [9] – these will therefore be used throughout this chapter (Table 8.1).

Further confusion is added by the fact that many observational trials rely on patient self-reporting of statin side effects without objective proof of the muscular origin of these symptoms. Non-neuromuscular side effects, such as tendinopathies or arthropathies, with associated pain are fairly common and have been reported by up to 24 % of patients in the PRIMO study, an observational investigation [10].

8.3 Epidemiology of Statin-Related Myotoxicity

Information on statin-associated muscle symptoms (SAMS) has been derived from both controlled clinical trials and observational studies of statins in everyday clinical use. Whilst the latter indicates that 7–29 % of patients complain of SAMS [5, 10–12], the randomized controlled trials yield very different results: in RCTs, adverse event rates are similar in statin and placebo groups [1, 13, 14]. A large meta-analysis of 42 randomized trials covering almost 60,000 patients [15] found that 12.7 % reported muscle problems in the statin groups vs. 12.4 % in the placebo groups, a non-significant difference. In two studies, CARDS and SPARCL, the placebo groups even had a higher rate of myalgia than the verum group [15]. Only two trials [16, 17], however, had questioned participants systematically about muscle symptoms and reported an incidence for myalgia of 3 % [16] and 9.4 % [17], respectively.

The frequency of myopathy, as defined above, was much lower at less than 0.5 % [1, 18] with standard doses of statins, but extended up to 2 % at high-dose treatment

Table 8.2 Frequency of statin-associated muscle problems

	Verum groups	Placebo groups	Significant
Any muscle symptom			
(Meta-analyses)	12.7 %	12.4 %	No
(Observational trials)	7–29 %	–	–
Myopathy (CK >3x ULN)	0.5 %	0.3 %	Yes
Myopathy (CK >10x ULN)	0.2 %	0.16 %	No
Rhabdomyolysis	0.03 %	0.02 %	No

Adapted from Kjekshus et al. [16]

Table 8.3 Risk factors for statin myopathy

Patient features	Drug features
Age> 80 years	Statin dose
Comorbidity (renal, hepatic, hypothyroidism, diabetes, trauma, neuromuscular disease)	Type of statin (lipophilicity) *Higher risk*: simvastatin, lovastatin, atorvastatin *Lower risk*: pravastatin, fluvastatin, rosuvastatin
Diet (grapefruit juice)	Interacting drugs:
Pre-existing hyperCKemia	CYP3A4 inhibitors (macrolides, azoles, HIV-drugs, amlodipine, amiodarone, cyclosporine, tetracyclines)
Vitamin D deficiency	Fibrates, gemfibrozil, niacin
Previous statin intolerance	Steroids
Alcohol abuse	
Genetic predisposition (SLCO1B1, CYP3A4 polymorphisms)	

(atorvastatin 80 mg) [19, 20]. Thus, the overall frequency of myopathy is low, but increases at higher statin doses and with concomitant use of interacting medication (Table 8.2). Moreover, in the above meta-analysis [15], no myopathy was reported with fluvastatin, which was also associated with the least number of muscle symptoms in the PRIMO study [10].

Rhabdomyolysis, as defined above, was even rarer with an incidence of 0.03 % in two meta-analyses [15, 21] and its frequency was not different from the placebo groups (0.02 %) (Table 8.2). In all trials, rhabdomyolysis was not seen in patients who did not have additional risk factors (Table 8.3).

Why do the outcomes of clinical trials not reflect clinical practice, where SAMS are reported much more frequently (Table 8.2)?

First, clinical trials usually exclude patients with a history of muscle problems and other risk factors for myopathy. Second, most statin trials were not primarily designed to assess muscle complaints. Third, the lack of a placebo group in many observational studies often precludes verification of a causal relationship between statins and muscle symptoms, which are therefore overestimated. This particularly applies to patients with anxiety or depressive disorders who frequently complain of muscle soreness. Fourth, physical activity, an important trigger of "statin myopathy", has not been taken into account in most studies.

Considering the results from both randomized and observational studies, one may conclude that myalgias are not uncommon (2–10 %), but clinically significant myopathy with CK elevations and weakness is much rarer (~0.5 %) and rhabdomyolysis is even less frequent (<0.05 %) and almost always associated with concomitant medication.

8.4 Pathogenesis of Statin-Induced Myopathy

Several mechanisms have been proposed for the myotoxic effects of statins. Inhibition of the mevalonate pathway, the central step in cholesterol biosynthesis, by statins also interacts downstream with other important pathways (Fig. 8.1):

- Impaired production of coenzyme Q10, which forms an essential part of the respiratory chain, may lead to mitochondrial dysfunction. Although statin therapy has been shown to decrease CoQ10 plasma levels [22], the results of muscle CoQ10 analyses have been inconclusive [23, 24]. Some, but not all, patients show mitochondrial pathology in muscle biopsies, such as COX-negative and ragged-red fibres [24, 25], and depletion of mtDNA [26].
- Secondary mitochondrial changes, such as altered membrane fluidity, or changes in calcium homeostasis probably play a minor role.
- Prenylation of proteins is implicated in cell differentiation, signalling and proliferation and is also involved in immune responses. Impaired prenylation will therefore ultimately increase apoptosis. Since inhibition of cholesterol biosynthesis downstream of HMG-CoA reductase at the level of squalene synthase does not cause myotoxicity, impaired protein prenylation is regarded by many as being one of the most important pathogenic mechanisms [27].
- A subgroup of statin-associated myopathy may be triggered by an autoimmune process targeted against HMG-CoA reductase, clinically manifesting as a necrotizing myopathy [28]. However, in a large cohort of patients with HMGCR-antibodies, only 2/3 were ever exposed to statins [29]; interestingly, the latter responded better to immunosuppressive therapy than the statin-naïve patients [30]. The antibody was never found in asymptomatic statin users.
- Genetic predisposition to statin myotoxicity may be caused by pathogenic heterozygous variants in muscle disease-related genes [31]. These include CPT2-deficiency, Pompe disease, McArdle disease, Lipin1-deficiency and malignant hyperthermia. The most significant associations of statin myopathy with genetic polymorphisms have been reported for a hepatic transporter, encoded by SLCO1B1 [32], and for genetic variants in the detoxifying cytochrome P450 system [33]. A particular SLCO1B1 polymorphism is associated with an 18 % risk of developing a statin myopathy in homozygotes, a 3 % risk in heterozygotes and a 0.6 % risk in wild-type carriers [32]. A further association was verified for polymorphisms in the CoQ2-gene, which is involved in CoQ10 biosynthesis [34].

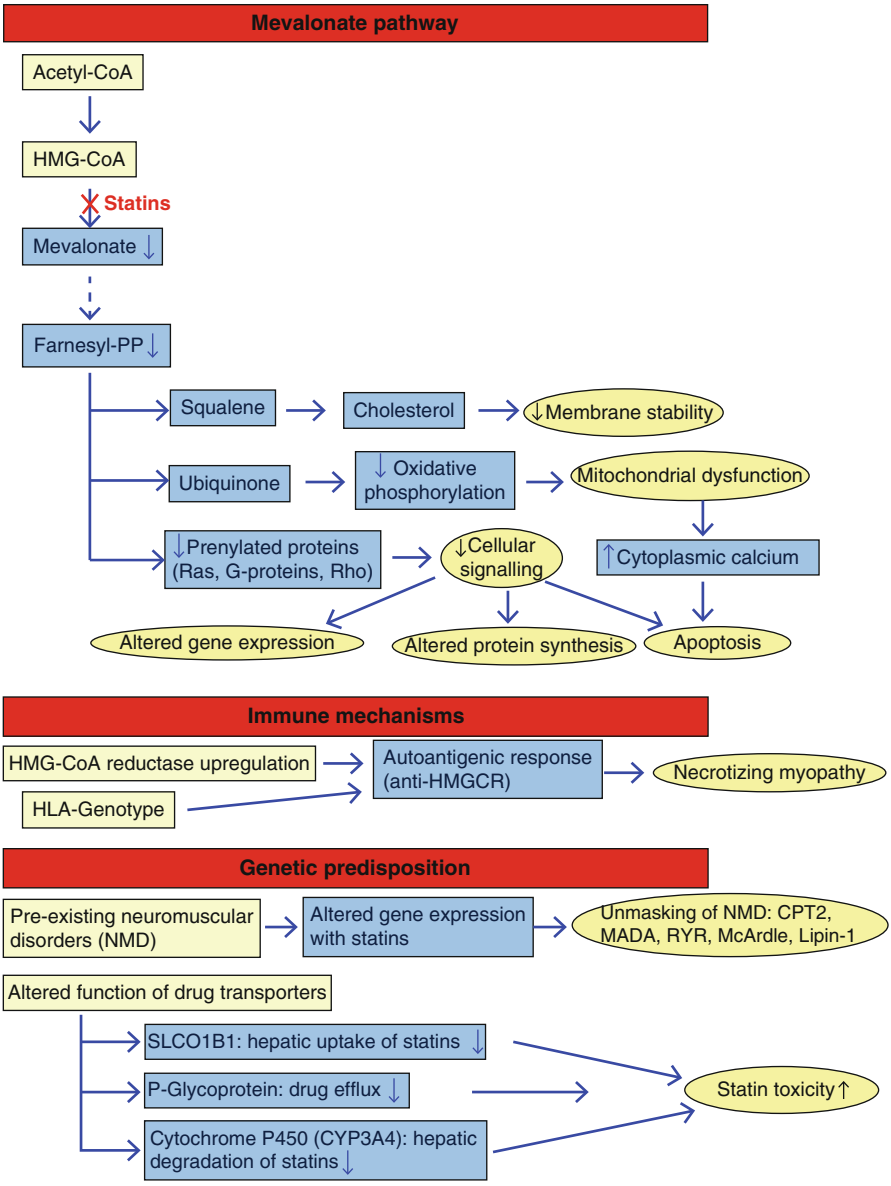

Fig. 8.1 Pathogenic mechanisms of statin myotoxicity

It should, however, be kept in mind that the benefit of reduced cardiovascular mortality far outweighs the risk of statin-related myopathy, even in those with the highest genetic risk known so far, i.e. the SLCO1B1 variants. Therefore, routine genotyping cannot be recommended.

8.5 Clinical Evaluation of Suspected Statin Myopathy

8.5.1 Clinical Features

Statin-induced myalgia and myopathy typically present as proximal, symmetric muscle pain and/or weakness, especially in the legs; nocturnal cramping is also common [17, 35]. The mean duration of statin therapy before symptom onset was 6 months; in 1/3 of patients, symptoms started within 1 month [35]. The mean interval to recovery after cessation of treatment was 2 months; 57 % of patients reported resolution of symptoms after 1 month and 93 % after 6 months [35]. The symptoms appear more frequently in exercising individuals and are often triggered by physical activity [10].

If symptoms persist for more than 6 months after discontinuation of the statin, alternative causes should then be investigated, i.e. underlying necrotizing or metabolic myopathies or heterozygous genetic variants thereof (→ 8.4).

A proportion of statin users shows an asymptomatic elevation of CK, usually <4x ULN, which resolves quickly after withdrawal of the drug. Some of these patients have mild morphological changes in a muscle biopsy [36].

Rhabdomyolysis, the most severe form of statin intolerance, is very rare (<0.1 %) and usually occurs with short delay after initiation of statins. It is characterized by severe muscle pain, weakness, very high CK and may lead to renal failure.

8.5.2 Diagnosis and Monitoring

The diagnosis of statin myotoxicity is usually straightforward and is based upon the temporal correlations of clinical symptoms and CK levels with initiation and termination of statin therapy (→ 8.5.1); sometimes a rechallenge of statin exposure may be necessary to firmly establish statin intolerance.

Current European guidelines [2] recommend to obtain a baseline CK in case symptoms develop, but there is no need for routine monitoring of CK, unless problems arise. In this case, CK should be measured to evaluate the severity of muscle damage and to decide whether treatment should be discontinued.

Electromyography, nerve conduction studies and MR imaging may be normal or show non-specific abnormalities; their main purpose is exclusion of other differential diagnoses.

Muscle biopsy is not routinely performed [2], except in those with persisting symptoms or hyperCKemia despite cessation of statin medication. It is then necessary to investigate for autoimmune necrotizing myopathy, because this specific complication requires immunosuppressive therapy [30].

8.5.3 Risk Factors for Statin Myopathy

The risk factors predisposing to statin-induced myopathy or myalgia can be classified into patient-related and drug-related factors (Table 8.3):

Amongst the patient characteristics, increased physical activity is probably the most important aspect to consider when statin patients complain of acute muscle symptoms [10, 37]. Other important risk factors are comorbidities, genetic polymorphisms and ethnicity (Asian descent carries a 3–4x increased risk).

In ALS, high cholesterol levels are associated with prolonged survival [38], and it seems prudent to stop statins in patients who develop ALS. Statins are also known to trigger muscle symptoms in cases of pre-existing muscle disease (→ 8.4), including myasthenia gravis, but at least in the latter case statin treatment is still regarded as safe, if required.

Amongst the drug characteristics, the statin dose is probably the most important predictor of side effects. Data from the SEARCH trial [19], comparing 80 mg of simvastatin with 20 mg of simvastatin, showed a minor decrease in efficiency with the lower dose but a 40 times higher frequency of myopathy with the higher dose. On the basis of this data, the FDA recommended not to use the higher dose any longer. The risk of myopathy appears to be lower with hydrophilic statins (fluvastatin, pravastatin, rosuvastatin) compared to lipophilic statins (simvastatin, lovastatin), because penetration into muscle tissue is related to lipophilicity. In the PRIMO study [10], fluvastatin appears to carry the lowest risk for myopathy.

In common with half of all the drugs which we take, most statins are metabolized by the cytochrome P450 (CYP3A4) system. Concurrent medication which inhibits CYP3A4 (Table 8.3) will therefore reduce clearance of CYP3A4-dependent statins (simvastatin, lovastatin, atorvastatin), thus increasing toxicity. Fluvastatin, pravastatin and rosuvastatin are metabolized via CYP2C9 and demonstrate less interactions with other drugs.

Increased susceptibility to myopathy is also seen in combination with fibrates [39], in particular gemfibrozil, niacin and drugs which are independently myotoxic (steroids, cyclosporine, zidovudine).

8.6 Management of Statin-Induced Myopathies

Following a recent consensus statement of the European Atherosclerosis Society [39], the first step should always be to reassess the indication for statin use and to evaluate whether the risk factors can be minimized (Table 8.3). Thereafter, the following scenarios are possible:

8.6.1 Creatine Kinase <4x ULN

(a) Tolerable symptoms:
The statin may be continued; symptoms and CK should be monitored regularly and used as guideline for possible discontinuation of treatment.

(b) Intolerable symptoms:
The statin should be discontinued regardless of CK levels, because compliance for taking the drug will be low.

If symptoms persist after a 4-week washout phase and the risk-benefit ratio warrants further treatment, the following options exist:

- Restart with lower dose of statin [19]
- Restart with less myotoxic statin (pravastatin, fluvastatin, rosuvastatin) [10]
- Try alternate-day dosing with long half-life statin (atorvastatin)
- Vitamin D deficiency should be corrected: some evidence supports vitamin D supplementation [40].
- CoQ10 administration (600 mg/d): a recent large meta-analysis [41] failed to show any benefit of CoQ10 supplementation.

If symptoms improve after discontinuation of the statin, treatment can be recommenced with either the same statin dose or according to the above protocol.

8.6.2 Creatine Kinase >4x ULN and <10x ULN

The statin should always be stopped and the need for treatment be reassessed. If considered necessary the statin may be restarted following the above options, once CK and symptoms have normalized. CK levels should then be continuously monitored and that particular treatment regimen be stopped if the levels exceed 10x ULN. An alternative regimen may be tried again or a non-statin-based therapy may be employed.

If CK persists to be high, the possibility of an underlying neuromuscular disease, in particular a necrotizing myopathy (→ 8.5.2), should be considered.

8.6.3 Creatine Kinase >10x ULN

Statin treatment should be stopped and renal function and risk factors be checked. If the CK level returns to normal, a second attempt with a lower dose of a different statin may be undertaken with careful monitoring of CK.

In case of rhabdomyolysis (affecting renal function), no further statins should be tried, and a non-statin-based lipid-lowering therapy be considered.

Following this algorithm (8.6.1–8.6.3), 43 % of patients with statin intolerance were eventually able to continue statin treatment with another lower-dose statin [35].

8.6.4 Complete Statin Intolerance

Even though rare (<0.2 % of statin users), alternative non-statin-based lipid-lowering therapies may become necessary in case of complete statin intolerance.

Ezetimibe, an intestinal cholesterol uptake inhibitor, is the first choice for these patients and may sometimes permit the use of statins concomitantly at low enough doses to limit muscle damage.

Other less efficient alternatives are bile acid sequestrants (cholestyramine), fenofibrate or niacin, which should be used in combination with ezetimibe.

Very recently, PCSK9 inhibitors (alirocumab) which target LDL receptors for degradation, were approved by the FDA and EMA. Studies have consistently shown large LDL reductions with a very low rate of muscle symptoms [42] which makes these drugs a good alternative for statins.

Finally, LDL apheresis may pose an option for statin-intolerant patients with very high LDL cholesterol levels, but this is reserved for the most severe cases.

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Myasthenia Gravis

9

Amelia Evoli and Raffaele Iorio

9.1 Introduction

At the normal NMJ, the motor nerve ending (presynaptic region) and a specialized portion of muscle membrane (postsynaptic region) are juxtaposed, being separated by a ~50 nm width, termed synaptic cleft. This space comprises the basal lamina that has a central role in NMJ formation, securing a stable concentration of synaptic proteins, both nerve derived (as agrin, neuregulin) and muscle derived (as laminin β-2) and of the enzyme acetylcholinesterase (AChE) [1]. AChE is expressed in an asymmetric form composed of tetramers of catalytic subunits attached to a collagen tail ColQ that anchors the enzyme through binding both perlecan and the muscle protein MuSK (muscle-specific tyrosine kinase receptor) [2].

In the nerve terminal, synaptic vesicles accumulate at the active zones where P/Q-type voltage-gated calcium channels (VGCC) are clustered. Each vesicle contains 5000–10,000 molecules of acetylcholine (ACh) and is referred to as a quantum. The postsynaptic membrane is folded into secondary synaptic folds which greatly increase its area. At the crest of the folds, the acetylcholine receptors (AChRs) are assembled at a high density (10,000–20,000/μm^2), anchored to the dystroglycan complex through rapsyn [1]. The AChR clustering and the maintenance of NMJ require MuSK activation by agrin through its coreceptor Lrp4 (low-density lipoprotein receptor protein 4) [3].

When an action potential (AP) depolarizes the nerve terminal, the opening of VGCCs results in a rapid increase of the intra-nerve Ca^{2+} concentration, which triggers the exocytosis of 50–300 quanta. The binding of two ACh molecules leads to a conformational change in the AChR and opens the ion channel; the influx of Na^+ results in a local membrane depolarization, end plate potential (EPP), which is

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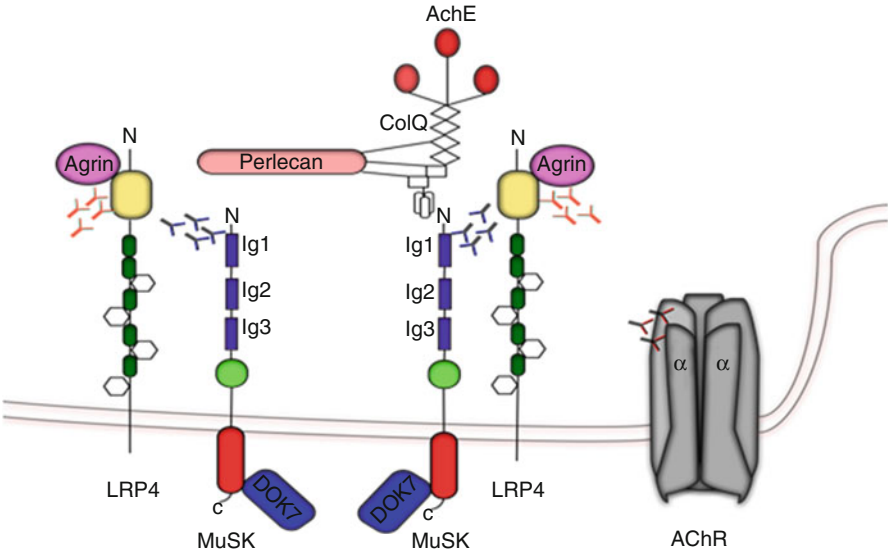

Fig. 9.1 Antibody targets in myasthenia gravis: structure and interactions with related molecules

greatest in the depths of secondary folds where voltage-gated sodium channels (VGSC) are highly concentrated . When the EPP is adequate to open these channels, a muscle AP ensues.

At the normal NMJ, the EPP largely exceeds the threshold for the generation of a propagated muscle AP. This corresponds to the safety factor of neuromuscular transmission (NMT) that depends on presynaptic (amount of quanta released per each nerve depolarization) and postsynaptic (AChR and VGSC density) factors. NMT diseases are characterized by an alteration, generally a reduction, of the safety factor.

Myasthenia gravis (MG), the most common of these disorders, is caused by antibodies (Abs) to different proteins of the postsynaptic membrane (Fig. 9.1). Abs to the AChR are detected in the great majority of patients, 5–8 % have Abs against MuSK, and a lower proportion of patients harbor Abs to Lrp4 [4]. The autoimmune attack causes morphologic and functional alterations, responsible for NMT impairment, which results in fatigable weakness of voluntary muscles.

9.2 Epidemiology

MG affects all races and can onset at any age, from the first year of life to the nineties. Epidemiological investigations have mostly been focused on the AChR-positive disease (AChR-MG). On the whole, these studies show a broad variability both in incidence, which varies from 4.3 to 18.0 per million, and in prevalence rate, ranging from 70.6 to 163.5 per million [5]. In Western countries, AChR-MG typically shows

a bimodal age of onset, with predominance of women among early-onset cases (between the second and fourth decade) and of men in a more advanced age; childhood MG with purely ocular symptoms is common in Asian populations.

The positivity rate of MuSK Abs in AChR-negative patients varies across populations, with higher rates in Mediterranean countries in Europe and among Afro-American patients in the USA [6]. In two nationwide studies, MuSK-MG prevalence was 1.9 per million in the Netherlands and 2.9 per million in Greece [5]. The disease shows a marked prevalence in women with an average age at onset in the mid-thirties.

The positivity rate of Lrp4 Abs in AChR- and MuSK-negative patients varies in different studies. In a large series of 635 patients, the overall frequency of Lrp4 Abs was 18.7 %, with variations among populations from different countries [7]. Lrp4-MG appears to be prevalent in women (male/female ratio of 1:2) with mean age of onset in the fourth decade.

9.3 Pathogenesis

9.3.1 MG with Abs to AChR

The AChR is a pentameric ion channel with a stoichiometry $2\alpha1\beta1\gamma\delta$ in embryonic/denervated muscle and $2\alpha1\beta1\varepsilon\delta$ in normal adult muscle. Although AChR Abs are polyclonal and can recognize all receptor subunits, epitope mapping studies have shown that a high proportion of patients have serum Abs to the so-called main immunogenic region (MIR) on the extracellular domain of α1 subunits [8]. MIR Abs are highly pathogenic and their serum level was shown to correlate better with disease severity than total AChR Ab titer [8].

AChR Abs mostly belong to IgG1 and IgG3 subclasses and impair NMT through complement-mediated destruction of the postsynaptic membrane, increased AChR degradation by receptor cross-linking, and competition with ACh binding [4]. Their pathogenicity has been fully demonstrated in experimental MG studies, both by active immunization and patients' IgG injection.

AChR-MG is frequently associated with alterations of the thymus, the organ where T cell maturation and establishing of central tolerance occur. Most patients with early-onset MG (age of onset <50 years) have thymic follicular hyperplasia characterized by expansion of the perivascular spaces with prominent B cell and plasma cell infiltration and germinal center formation. The hyperplastic thymus is thought to be the site where the autosensitization against AChR occurs and Ab production is initiated [9]. An intra-thymic inflammatory milieu, possibly induced by infectious agents, together with immune-regulatory defects and a predisposing genetic background concur to the establishing of the autoimmune response [10]. Early-onset AChR-MG is associated with human leukocyte antigens (HLA) B8 and DR3 [10]. A thymoma is present in 10–20 % of AChR-MG patients, with the highest frequency between the fifth and seventh decades of life. Thymomas are tumors of thymic epithelial cells harboring variable proportions of nonneoplastic

lymphocytes. Thymomas associated with MG are prevalently of "cortical" types with a rudimental medulla and retain the capacity to export mature T cells [10]. Tumor tissue does not produce AChR Abs, but through a defective T cell, selection can contribute to MG pathogenesis by the export of autoreactive $CD4^+$ T cell and a reduced production of T regulatory cells [9]. Lastly, in patients with late-onset disease, the thymus parenchyma is mostly replaced by fat, even though some B cell infiltration and occasional germinal centers can be found [9].

9.3.2 MG with Abs to MuSK

MuSK is a transmembrane protein, made of an extracellular region consisting of three immunoglobulin-like (Ig-like) domains and a cysteine-rich domain, a transmembrane helix, and a cytoplasmic region harboring the kinase activity. MuSK activation by neuronal agrin triggers an intracellular signaling cascade leading to AChR and rapsyn clustering [3]; in addition, its binding to ColQ carboxyl-terminal anchors AChE to the basal lamina [2].

Abs to MuSK are prevalently IgG4 and target mostly the first two Ig-like domains in the extracellular region [11]. Although IgG4 does not activate complement and is relatively inefficient in cross-linking adjacent antigens, IgG4 MuSK Abs were found to correlate with disease severity in patients [12] and induced MG weakness when injected into mice [13]. These Abs were shown to interfere with MuSK-ColQ binding, causing a reduced AChE concentration at the synaptic cleft [14], and to prevent MuSK-Lrp4 binding, thus inhibiting agrin-induced MuSK activation [15]. In addition, immunized animals showed a presynaptic dysfunction as lack of compensatory increase in ACh release, which is a homeostatic response in AChR-MG [13].

The thymus does not seem to be involved in the disease pathogenesis, as pathological examination of specimens from thymectomized patients did not show hyperplastic changes and the association with thymoma has rarely been reported [9]. An association with DR14/DR16 and DQ5 has been observed in these patients [10].

9.3.3 MG with Abs to Lrp4

Lrp4 belongs to the low-density lipoprotein (LDL) receptor family and is expressed in several tissues. At NMJ, Lrp4 acts at both pre- and postsynaptic levels, as it enhances MuSK activation through binding agrin and, in a retrograde manner, stimulates nerve terminal differentiation [16]. Lrp4 is a transmembrane protein consisting of a large extracellular region with multiple LDL repeats, epidermal growth factor (EGF)-like and β-propeller domains, a transmembrane helix, and a short cytoplasmic region. The extracellular region binds both agrin and MuSK [17].

Abs to Lrp4 are mostly IgG1 and were shown to interfere with agrin binding [18]. Immunization with Lrp4 ectodomain induced muscle weakness, AChR cluster fragmentation, and both pre- and postsynaptic NMT dysfunction [19]. A thymoma

has never been found in Lrp4-MG. Though some of these patients were reported to have thymic hyperplasia, there is no convincing evidence of a pathogenic link with the thymus.

In distinct studies, Abs to agrin [20], ColQ [21], and cortactin [22] have been reported in MG patients, often in association with either AChR or MuSK Abs. Their pathogenicity has not been proved, so far, in animal models.

9.4 Clinical Features

The hallmark of MG is fatigable weakness of skeletal muscles. Fatigability is the most consistent feature; weakness is usually present on examination but, in mildly affected cases, may be evident only on exertion. Clinical fluctuations, both daily and over longer periods, are typical. Although all voluntary muscles can be affected, some muscle groups are more commonly involved than others, and clinical presentation is quite characteristic. However, there is a marked variability in weakness extension and severity, from purely ocular symptoms to severe life-threatening disease.

The extrinsic ocular muscles (EOM) are affected in the great majority of patients, and ptosis and diplopia are the most common presenting symptoms. Ptosis is generally asymmetrical (Fig. 9.2, section a) and frequently alternating; it typically fluctuates in severity over short periods. Binocular diplopia can be caused by weakness of a single muscle or of any EOM combination. It is usually intermittent in the early stages of the disease and then tends to become constant. The association of variable diplopia and asymmetrical ptosis is useful in differentiating ocular MG from oculopharyngeal dystrophy, chronic progressive ophthalmoplegia, and thyroid myopathy.

In around 15 % of patients, MG remains confined to EOM; in the other cases, usually within 2 years from the onset, weakness spreads to other muscle groups [23]. Facial weakness is very common, with inability to close the eyes tightly and to whistle and development of a vertical smile (Fig. 9.2, section b). In limbs, proximal muscles are prevalently involved; weakness of finger extensors is relatively frequent, while ankle dorsiflexion is more rarely affected. Weakness of "bulbar" muscles (masseter, tongue, pharyngeal, and laryngeal muscles) is responsible for

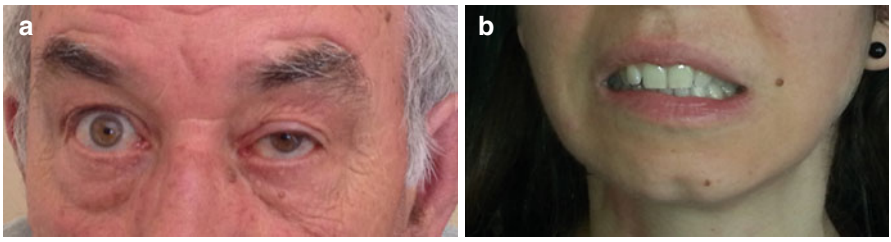

Fig. 9.2 Asymmetrical ptosis in (**a**). Facial weakness with a vertical smile in (**b**)

difficulty in chewing, dysphagia with regurgitation of fluids through the nose, and dysarthria (nasal speech). Among axial muscles, both neck flexors and extensors are involved. Respiratory failure requiring assisted ventilation (the so-called myasthenic crisis) is due to weakness of the diaphragm and intercostal muscles together with upper airway obstruction by bronchial secretions. Crises occur in 15–20 % of patients, and in spite of improvement in MG treatment and critical care, the related mortality rate is still 5 % [24]. Although AChR-MG encompasses the whole clinical spectrum, weakness pattern shows some differences in patient subgroups. Leg muscle involvement is often predominant in younger patients; bulbar and neck weakness is frequent in late-onset disease; early respiratory crises are more common in thymoma-associated MG.

MuSK-MG is nearly always a generalized disease. In most patients, clinical phenotype is characterized by a prevalent involvement of bulbar and axial muscles, with dysarthria, dysphagia, and weakness of the tongue, facial, and neck muscles. Limbs are mildly affected and can be totally spared [25]. Ocular symptoms are common at presentation, but diplopia is generally transient and ptosis is less asymmetrical than in AChR-MG. Myasthenic crises and muscle atrophy are more frequent than in other forms of MG [26]. Muscle atrophy mainly affects facial, tongue, and masseter muscles and can lead to fixed weakness with permanent dysarthria and a myopathic face. Lastly, daily symptom fluctuations are uncommon in these patients, who, however, suffer from frequent MG deteriorations especially in the first years from the onset [26].

The characteristics of Lrp4-MG are not fully defined, but the clinical phenotype in these patients seems to be similar to AChR-MG. In the largest population reported so far, around 22 % of patients had purely ocular symptoms, and those with generalized MG were prevalently affected by mild to moderate weakness [7].

9.5 Diagnosis

Once MG is suspected on clinical grounds, diagnosis confirmation is achieved through serum Ab detection, electrophysiological evidence of a postsynaptic defect of NMT, and clinical response to acetylcholinesterase inhibitors (AChE-I).

9.5.1 Serum Ab Assay

AChR Abs are detected in 85–90 % of patients with generalized MG, in 50 % of those with ocular disease, and in nearly all cases of thymoma-associated MG [27]. Therefore, these are the first Abs to be tested when MG is suspected. All patients with negative results on this assay should be tested for MuSK Abs, taking into account that the latter are very rarely associated with isolated ocular symptoms. AChR and MuSK Abs are very specific [27], and, in practice, their detection in patients with congruent symptoms confirms the diagnosis.

The positivity rate of AChR Abs has been further increased by the demonstration that some patients have serum IgG able to bind to AChRs when concentrated on cell

surface, as those at the NMJ. With a cell-based assay (CBA), serum Abs to "clustered" AChR were found in 50–60 % of patients negative on the standard assay, including some ocular MG cases [28].

Abs against Lrp4 have been detected with different techniques at frequencies varying from 3 to 50 % of AChR- and MuSK-negative samples. The recent report of these Abs in high proportion of patients with amyotrophic lateral sclerosis (ALS) casts doubt upon their specificity for MG [29].

The diagnostic value of other Abs is not defined. Moreover, while the standard radioimmunoassay for AChR and MuSK Abs is largely available, the other Abs can be tested in selected laboratories.

AChR-MG is associated with striated muscle (striatonal) Abs that recognize intracellular proteins, as titin and the ryanodine receptor (RyR). These Abs are strongly associated with thymoma (titin Abs are positive in 95 % and RyR Abs in 70 % of thymoma patients) and are present in nearly 50 % late-onset non-thymoma patients, while they are very uncommon in early-onset MG. Striatonal Abs are not diagnostic of MG and presumably not pathogenic, but are markers of thymoma in younger MG patients, and seem to correlate with disease severity [30].

Abs to Kv1.4 that target the muscle voltage-gated potassium channel were found to be associated with severe MG and myocarditis in Japanese patients [31].

9.5.2 Electrophysiological Studies

Repetitive nerve stimulation (RNS) is the most frequently used technique in the electrophysiology of NMT. In MG, low-frequency (2–3 Hz) RNS is typically associated with a decrement, greater than 10 %, of the compound muscle AP (CMAP) amplitude between the first and fourth or fifth stimulus. RNS diagnostic yield depends on testing weak muscles and is related to weakness pattern and severity. The rate of positive results is close to 75 % in patients with generalized MG and less than 50 % in those with isolated ocular symptoms [32]. In MuSK-MG, on account of the predominant bulbar involvement, diagnostic sensitivity is low, unless facial muscles are examined [33]. A decremental response on low-frequency RNS is not specific for MG as it is found in other primary disorders of NMT and in some patients with ASL or radiculopathy [32].

Single fiber electromyography (SF-EMG) records APs from single muscle fibers and measures jitter during voluntary activation or nerve stimulation. In volitional SF-EMG, jitter corresponds to the time interval variations between pairs of APs from two or more muscle fibers belonging to one motor unit. When NMT is impaired as in MG, increased jitter and "impulse blocking" (when EPP does not reach the threshold to generate an AP) occur [32]. SF-EMG is the most sensitive diagnostic test for MG, as, provided that appropriate muscles are examined, positive results are recorded in 98 % of cases, including patients with ocular myasthenia [34] or MuSK-MG [26]. However, an increased jitter is far from specific as, apart from other diseases of NMT, it can be found in neurogenic and myopathic conditions [27].

9.5.3 Pharmacological Test (Response to AChE-Is)

In MG, AChE-Is improve NMT by increasing the lifetime of ACh that can bind repeatedly to AChRs. Short-acting agents, as edrophonium chloride IV and neostigmine IM, are generally used for diagnostic purposes. Response should be evaluated on selected weak muscles and compared with reaction to placebo. With these prerequisites, a definite clinical improvement, although not specific, strongly supports the diagnosis. As edrophonium injection can be associated with bronchoconstriction and severe bradycardia, atropine should always be kept at reach.

In MG the overall rate of positive responses of edrophonium/neostigmine testing is 90 % [35]. However, in MuSK-MG, improvement upon AChE-I injection is much less common (50–70 %); side effects, such as muscle cramps and fasciculations, are frequent; and symptom worsening can be observed [26]. Cholinergic hypersensitivity in MuSK-MG can be ascribed to a relative deficiency of AChE at the synaptic cleft as a result of Ab interference with MuSK-ColQ binding [14].

A positive reaction to edrophonium/neostigmine test is observed in congenital myasthenic syndromes (CMS) and, less frequently, in Lambert-Eaton myasthenic syndrome. “False” responses have been reported in ALS and Guillain-Barrè syndrome [36].

Upon MG confirmation, all patients should undergo a radiological study of the thymus to rule out a thymoma, together with a screening for other autoimmune diseases (especially thyreopathies) and medical conditions that could interfere with treatment.

9.6 Treatment

Treatment decisions are based on weakness extension and severity, pathogenic aspects (associated Abs, thymus pathology), and patient’s characteristics. Current treatment, although largely unspecific, has dramatically reduced mortality and restored lifestyle to normal in many patients.

9.6.1 Symptomatic Treatment

Oral AChE-Is represent the first-line treatment, pyridostigmine bromide (Mestinon) being the agent most commonly used. In general, MG patients respond to AChE-Is, even though a satisfactory control of symptoms can be achieved in a minority of cases. Treatment is usually well tolerated and adverse effects (gastric discomfort, diarrhea, salivation, and cramps) are mild and can be reversed by dose reduction. On the other hand, MuSK-MG patients often show both unresponsiveness to and intolerance of AChE-Is, as – with Mestinon standard doses – they develop signs of cholinergic hypersensitivity [37] that may progress to weakness worsening (due to depolarization block) and respiratory failure [26]. Cholinergic crises are currently very rare in AChR-MG, which are associated with AChE-I overdosage [27].

Both 3,4-diaminopyridine and albuterol proved effective and well tolerated in MuSK-MG animal models [38]. These agents have not been tested in patients. A recent case report suggests that 3,4diaminopyridine may improve MuSK-MG [39].

9.6.2 Thymectomy

Although thymectomy has been in use for many decades, its efficacy has never been ascertained in controlled study (the first randomized trial is ongoing).

Thymectomy is indicated in all thymoma cases. In the absence of a thymoma, it is recommended in patients with generalized MG as an option to increase the probability of remission and improvement [40]. In most centers, it is performed in subjects with early-onset AChR-MG, in whom the removal of a hyperplastic thymus is associated with a high rate of drug-free remission. Patients with late-onset MG show a less satisfactory response, and the indication to surgery in the other disease subtypes is controversial. In particular, in MuSK-MG clinical studies failed to show significant differences in outcome measures between thymectomized and unthymectomized patients [38].

Lastly, it is worth pointing out that thymectomy, even in patients with thymoma, is never to be considered an emergency treatment and should be performed once stable control of the disease has been achieved.

9.6.3 Short-Term Immunomodulation

Plasma exchange (PE) and intravenous immunoglobulin (IVIg) that induce a rapid albeit temporary improvement are mostly used in the treatment of MG exacerbations. In addition, both (in particular IVIg) are used as periodic treatment in selected cases unresponsive to immunosuppression. In two randomized trials, PE and IVIg were shown to have comparable efficacy in an acute setting [41, 42]; there is no evidence for IVIg superiority over steroids in chronic treatment.

PE protocol consists of three to five exchanges performed every other day. Serious complications are mainly related to central venous catheters [43]. Semi-selective immunoadsorption, which does not remove albumin and coagulation factors, can be a safer alternative in patients requiring frequent PE. IVIg is administered at a dose of 400 mg/kg/day for 2–5 days. It is generally well tolerated, although serious complications have occasionally been reported [44].

9.6.4 Immunosuppressive Therapy

Immunosuppressive therapy is performed when symptoms are not adequately controlled with AChE-Is. The initial goal is to improve MG as quickly as possible; thereafter, medications should be reduced to the minimum effective dose to minimize side effects. From these principles, steroids are the first treatment because of their rapid-onset effect; in chronic administration immunosuppressants are associated as steroid-sparing agents.

9.6.4.1 Steroids

Prednisone and prednisolone are the agents mostly used in MG. They are generally administered on a daily basis at the start of treatment, then shifting to an alternate-day regimen with slow dose reduction. In most cases, ocular myasthenia can satisfactorily be managed with low-dose prednisone (25 mg/day as starting dosage), while in patients with generalized MG, higher doses (0.75–1 mg/kg/day) are employed. As steroids may induce a temporary MG deterioration, in patients with generalized disease, treatment should be started in the hospital, and PE or IVIg may be given to reduce symptom severity. The association of high-dose steroids plus PE or IVIg is also the standard treatment for severe bulbar symptoms or respiratory crises.

Steroids are effective in around 80 % of MG patients [45], but symptom relapses are frequent on dose tapering and chronic administration entails the risk of a number of side effects.

9.6.4.2 Immunosuppressants

Several immunosuppressants are used in the treatment of MG and appear to be effective in the great majority of patients, although class I evidence is still limited [45, 46]. All these agents have a long-latency effect; they can be administered in combination with steroids from the beginning and can replace prednisone in long-term treatment. Close monitoring of side effects is recommended, and because of the potential risk of infections and malignancy, the lowest maintenance dose should be determined in each patient [27].

In many countries, the purine analogue azathioprine is the first choice immunosuppressant in MG, at a starting daily dose of 2.5–3 mg/kg and a maintenance dose of 1 mg/kg. Leukopenia and hepatotoxicity are the main adverse effects, which usually subside with dose reduction or withdrawal. As patients with thiopurine methyl transferase (TPMT) deficiency may develop severe bone marrow toxicity, TPMT activity should be measured before treatment.

Mycophenolate mofetil (MMF) inhibits T and B cell proliferation, with higher specificity than azathioprine for activated lymphocytes. At the standard daily dosage of 2–2.5 g, it resulted effective in retrospective analyses and open-label trials [46]. Although these results were not confirmed in two randomized studies [47, 48], MMF, also in view of its favorable toxicity profile, is largely used in patients unresponsive to or intolerant of azathioprine.

Of calcineurin inhibitors, both cyclosporine and tacrolimus were shown to improve MG in small randomized trials [46]. The use of cyclosporine (at an initial dose of 4–6 mg/kg and a maintenance dose $\leq$3–4 mg/kg) is limited by side effects, as nephrotoxicity and hypertension [27]. Tacrolimus seems to be relatively safe at the doses used in MG and can be used as third-line drug [46]. In a recent single-blinded study, methotrexate was found to be effective as steroid-sparing agent, with similar efficacy and tolerability to azathioprine [49]. The use of cyclophosphamide on account of significant toxicity is mostly reserved to patients with severe refractory disease [46].

Immunosuppression in MG as in other autoimmune diseases has been rapidly evolving with the introduction of biologic drugs. In case reports and observational

studies, rituximab, a chimeric monoclonal Ab (mAb) that depletes B cells, was found to be effective and well tolerated in MG, particularly in MuSK-MG [50]. Treatment with eculizumab, a humanized mAb that inhibits terminal complement, was associated with significant AChR-MG improvement in a randomized placebo-controlled trial [51]. New biologics are currently explored as potential therapies in MG. These agents are very promising in view of their specific immune targets. However, lack of controlled studies and safety concerns limit so far their use to MG refractory to conventional treatment.

Highlights

- Myasthenia gravis (MG) is a heterogeneous disease, in which different antibodies affect neuromuscular transmission.
- MG with antibodies to AChR is frequently associated with thymus pathology.
- MuSK antibodies should be tested in all AChR-negative patients.
- In patients without detectable antibodies, other conditions that can mimic MG must be carefully ruled out.
- Treatment strategy should be individualized, taking into account weakness severity, patient's characteristics, and pathogenic aspects.

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Acquired Autoimmune Rippling Muscles with Myasthenia Gravis

10

Carl F. Ansevin

10.1 Rippling Muscle Disorders

10.1.1 Inherited Rippling Muscle Disease

Rippling muscle disease is rare and inherited in an autosomal dominant pattern, although rarely it may be autosomal recessive. Rippling muscle disease (RMD) is a myopathy with symptoms and signs of muscle hyperexcitability. The disorder was first described in 1975 in five members of a Scandinavian family over three generations. They had stiffness after periods of rest and muscle mounding after percussion. The most unusual manifestation was the peculiar rolling phenomena in muscles particularly after percussion or stretch. There was no electrical evidence of myotonia and the pedigree suggested an autosomal dominant inheritance.

In 1989, six patients in two German families were described, and the disorder was aptly named rippling muscle disease because of the peculiar wavelike phenomena propagated across skeletal muscles. The rippling waves could be induced by stretch or percussion and traveled at 6 m/s which was about ten times slower than muscle action potentials. Because the phenomena was "electrically silent" (i.e., no evidence of myotonia), an intracellular calcium-mediated pathogenesis was postulated.

Most cases that are inherited are autosomal dominant, although a more severe homozygous autosomal recessive form has also been described.

10.1.1.1 Symptoms and Signs

The onset of symptoms in the inherited form is usually in childhood or early adulthood. Myalgia and pain appear to be the most common and distressing symptoms, while patients usually do not complain of the rippling phenomena. Pain is

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associated with cramps (both spontaneous and exertional) and can range from mild to severe. Interference with glycogenolysis due to problems with caveolae-associated phosphofructokinase has been postulated to contribute to the pain. Other signs include muscular hypertrophy, weakness, and percussion-induced muscle mounding and rapid contractions of muscle.

10.1.1.2 Caveolin 3

Five large German and Norwegian families with rippling muscles were reported in 2001, and the disorder was localized to chromosome 3p25 with missense mutations in the gene encoding caveolin 3 (CAV3).

Caveolin 3 is present in skeletal and cardiac muscle flask-like indentations in the cytoplasmic membrane called caveolae. Caveolae have roles in cytoplasmic membrane structure, membrane transport, and signal transduction.

Patients with the inherited form of RMD have decreased staining for caveolin 3 on muscle histochemistry.

10.1.1.3 Phenotypic Variability

Defects in the caveolin 3 gene had previously been shown to cause a form of limb-girdle muscular dystrophy. The rippling muscle phenomenon is the most common manifestation of caveolin 3 disorders, but there is significant phenotypic variability. Besides the previously described limb-girdle muscular dystrophy (now known as LGMD 1C), a distal myopathy and hyperCKemia have also been described. Patients with a cardiomyopathy and long QT interval have also been reported.

Phenotypic variability of genetic defects in the caveolin 3 gene is thus capable of causing both dystrophic and non-dystrophic neuromuscular problems. Over 30 defects in the caveolin 3 gene region have been described.

10.2 Acquired Autoimmune Rippling Muscles with Myasthenia Gravis

An autoimmune form of rippling muscles (ARM) associated with myasthenia gravis was first described in 1996. The initial patient was 56 years old when he developed myalgias and noticed the rippling muscle phenomena. He had nine siblings and no family history of RMD. His disorder was characterized by a stretch- and percussion-induced electrically silent (i.e., no myotonia or neuromyotonia) rippling phenomena that propagated across the muscles in an organized wavelike manner. The rippling muscle phenomena were identical to the rippling muscles described in the inherited forms of RMD, and like the inherited forms of RMD, he had muscular hypertrophy when initially examined. The patient was lost to follow-up for several years. When he finally returned, he had florid symptoms and signs of myasthenia gravis including ptosis, diplopia, severe weakness, and fatigability. He had positive acetylcholine receptor antibodies, decremental responses on repetitive nerve stimulation, a dramatic improvement with anticholinesterases, and a thymoma. His CPKs were elevated and he had inflammatory changes on muscle

biopsy. He was treated with plasmaphereses, thymectomy, steroids, and immunosuppression and improved.

In 2001, the next two cases of rippling muscles with myasthenia gravis were described and also responded to immunosuppressive therapy. To date, more than 15 cases of rippling muscles associated with myasthenia gravis have been described.

10.2.1 Symptoms and Signs

Like the initial case, subsequent patients have presented with myalgias and the stretch- and percussion-activated rippling muscle phenomena. These patients generally present in adulthood and have mildly elevated CPKs. There is no family history of neuromuscular disorders in the acquired autoimmune form of rippling muscles. The rippling muscle phenomena commonly present prior to the myasthenic symptoms. The rippling muscle phenomena can be so dramatic as to overshadow sometimes more subtle myasthenic symptoms such as mild ptosis or intermittent diplopia. Weakness too may be mild especially in the beginning.

10.2.2 Laboratory Findings

Mildly elevated CPKs are usually present. EMG in patients with both the inherited and acquired autoimmune rippling phenomena has been described as "electrically silent." This term has been used to differentiate the organized wavelike phenomena of rippling muscles from myotonia, neuromyotonia, and the more vermiform myokymia – all of which are quite noisy on electromyography. Inflammatory changes to variable degrees have been described on muscle biopsies. Patients have positive acetylcholine receptor antibodies which may be present even prior to developing clear symptoms of myasthenia.

Decreased caveolin staining on muscle biopsies of patients with rippling muscles associated with myasthenia gravis has been reported. Mosaic patterns of caveolin staining in patients with rippling but negative acetylcholine receptor antibodies have also been reported. Responses to immunosuppression have led others to postulate an immune-related mechanism in these sporadic disorders.

Sporadic forms of rippling muscles not associated with myasthenia gravis with benign courses have been seen but are not well described.

10.3 Autoantibodies with Acquired Rippling Muscles and Myasthenia Gravis

Myasthenia gravis is perhaps the best studied of all autoimmune disorders. Antibodies to the acetylcholine receptor at the neuromuscular junction are present in 85 % of those with the disorder, and MUSK antibodies are present in others. Because of the clear association of sporadic rippling muscles with myasthenia

gravis – a neuromuscular junction disorder – it is suspected that autoantigens to skeletal muscles may be responsible for the rippling phenomena.

It has long been known that patients with myasthenia gravis (MG) with and without thymoma have antibodies to skeletal muscles. Autoantibodies to an immunogenic area of titin have been described. Patients with ARM and MG also have autoantibodies titin, but this is to a different immunogenic region of titin than previously described. The area of titin to which these autoantibodies react is near the PEVK region of this huge protein. The PEVK region of titin provides elasticity to the muscle which allows it to be stretched. This region of the giant titin protein is near the Z band along which the T-tubules align. These autoantibodies have been cloned with a fusion protein and the product subsequently shown to react with the same immunogenic area of titin as the original autoantibodies. Studies of autoantibodies in patients with ARM and MG are ongoing.

10.4 Summary

The rippling muscle phenomenon is important to recognize for both clinical and scientific reasons. Clinically, the acquired autoimmune form of rippling muscles with myasthenia gravis has been well described, is treatable, and responds to immunotherapy. The association of rippling muscles with myasthenia gravis, a disorder localized to the neuromuscular junction with antibodies to the acetylcholine receptor, suggests that acquired rippling muscle is autoimmune and may be associated with separate but distinct autoantibodies. The rippling muscle phenomena is stretch and percussion activated in both acquired autoimmune rippling muscles with myasthenia gravis and inherited rippling muscle disease and "electrically silent" without myotonia or neuromyotonia. The stretch-activated rippling phenomena without clear electrical activity suggest the possibility of mechanosensitive channels in skeletal muscles. Inherited rippling muscle disease is associated with caveolin 3 mutations with significant phenotypic variability including a form of limb-girdle muscular dystrophy (LGMD 1C). The study of these mechanosensitive disorders may yield insight into muscle physiology and pathophysiology in a variety of neuromuscular disorders. Further study of both the genetic and autoimmune rippling muscle disorders may lead to a better understanding of the biochemistry and pathogenesis of muscle.

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Endocrinological Myopathies

11

Corrado Angelini

Disorders in endocrinological pathways lead to manifest acquired or endogenous forms of myopathy. Imbalance disorders of protein synthesis, electrolytes and carbohydrate can lead to severe forms of myopathies. The severity of endocrinopathies is important for the long-term outcome. In general, the main neuromuscular symptoms are proximal weakness, sometimes in addition to myalgia and fibre atrophy. Endocrine myopathies are usually reversed by treatment.

11.1 Thyroid-Related Myopathies

The initial descriptions of Graves and von Basedow included muscle weakness and atrophy in the clinical picture of thyrotoxicosis. Engel [1] reviewed the histopathological changes in thyrotoxic myopathy, thyrotoxic periodic paralysis and the clinical features of myasthenia gravis and thyrotoxicosis. The incidence of weakness in thyrotoxic patients is estimated to be about 67 %. In oriental races, 82 % of thyrotoxic patients over 40 years of age have weakness, compared with only 50 % of younger patients [2].

11.1.1 Thyrotoxic Myopathy

Thyrotoxic myopathy occurs in acute or chronic form [3]. Females tend to be more affected than males (ratio 3:1). In the acute form, the weakness is out of proportion to the visible muscle atrophy, and the thyrotoxicosis may be present for only a few weeks before the onset of weakness. In the chronic form, the thyrotoxicosis may be

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relatively mild and of long duration. Proximal muscle weakness is common (63 % of cases), while distal muscle weakness is uncommon (18 %). The EMG changes are myopathic and there is no elevation of serum creatine kinase, in contrast with hypothyroid myopathy. Cases of reversible motor neuron dysfunction in thyrotoxicosis were found by McComas et al. [4]. The main clinical signs of thyroid-associated ophthalmopathy include exophthalmus, eyelid retraction, double vision and optic neuropathy. Elevation and abduction are the most severely compromised eye movements. Magnetic resonance imaging reveals muscle enlargement in the majority of patients with Graves disease; orbital myositis might be distinguished from Graves ophthalmopathy by tendon expansion but less prominent muscle enlargement.

Physiological and Metabolic Mechanisms The changes are more prominent in slow muscle and result in a shift of the myosin ATPase activity to that characteristic of fast-twitch muscle; there is an increased rate of calcium uptake by the sarcoplasmic reticulum. Thyroid hormone might increase potassium efflux and causes potassium depletion in muscles. The loss of muscle potassium could account for depolarisation of thyrotoxic muscle fibres [5]. Thyrotoxic muscle tends to be depleted of glycogen. Thyroid hormones increase skeletal muscle heat production and the mitochondrial consumption of oxygen, pyruvate and malate. Although this increased oxidation and accelerated metabolism contributes to heat production in man, there is no direct evidence that thyrotoxicosis uncouples muscle mitochondria. Thyrotoxic patients also develop insulin resistance [6]. Satoyoshi and colleagues [2] found decreased creatine and creatine phosphate in hyperthyroid muscle. In addition, thyroid hormone stimulates protein degradation by increasing lysosomal protease activity, particularly cathepsins B and C [6].

Excessive amounts of thyroid hormone have the following effects (Table 11.1):

(a) Increased mitochondrial respiration, without uncoupling.
(b) Accelerated protein degradation.
(c) Enhanced calcium uptake by SR.
(d) Glycogen depletion and decreased glucose uptake may cause fatiguability.
(e) Shortening of contraction time derives from accelerated myosin ATPase and fibre-type adaptation.
(f) Thyrotoxicosis induces depolarisation of muscle fibres due to potassium depletion.

Table 11.1 Metabolic changes in muscle in hyper- and hypothyroidism

Hyperthyroidism	Hypothyroidism
High basal metabolic rate	Decreased oxygen consumption
Increased mitochondrial oxidation	Decreased oxidation
Glycogen depletion	High glycogen
Accelerated protein degradation	Reduced acid alpha-glucosidase
High cathepsin activity	Decreased protein turnover
	Decreased lysosomal proteases

All these mechanisms may contribute to the development of thyrotoxic myopathy in which histopathological changes are mild and consist only of simple muscle atrophy. Neuropathy associated with thyrotoxicosis is rare.

11.1.2 Thyrotoxic Periodic Paralysis

The first descriptions of the association of periodic paralysis with hyperthyroidism were by Japanese authors [7]. Similar cases have been reported in China [8]. There seems to be a racial susceptibility: in fact, thyrotoxic periodic paralysis (TPP) is much more frequent in Orientals and only sporadic cases have been observed in Caucasians. The attacks have many similarities to the familial hypokalaemic disorders. There is a profound weakness of the pelvic girdle and leg muscles lasting several hours. Cranial, speech and swallowing muscles are not affected. The most important criteria are the remission of paralytic attacks in TPP with appropriate antithyroid measures, including partial thyroidectomy if the attacks are due to a toxic adenoma. Hypokalaemia is due to migration of potassium from the extracellular space into the muscle cell [9, 10]. These authors found a constant positive arteriovenous difference of potassium during the development of paralysis in six patients with TPP.

In TPP, the total exchangeable potassium was reduced slightly, although there was no significant difference from the normal and thyrotoxic controls [9, 10]. Au and Yeung [11] found a periodic variation in the muscle SR calcium pump activity: both the calcium pump ATPase activity and the total amount of calcium uptake showed a decrease during TPP and a reversion to normal following the attack. The morphological abnormalities observed by Schutta and Armitage [12] consisted of a vacuolar myopathy. There was diffuse evidence of structural damage, with proliferation of the T system and vacuoles which were connected with it. It was concluded that these vacuoles do not represent dilatation of the SR but may represent sequestrated areas of focal myofibre necrosis. Atypical mitochondria, showing linear inclusions in the cristae, were also seen. Marked distension of the terminal sacs of SR with granular material is usually present. Electrophysiological changes in TPP include sarcolemmal depolarisation and inactivation of Na+channels leading to sarcolemmal inexcitability. The paradoxical depolarisation associated with hypokalaemia in TPP remains unexplained. TPP resolves in over 90 % of cases, with normalisation of thyroid function, while in acute paralytic attacks, administration of i.v. potassium chloride is the treatment of choice.

11.1.3 Hypothyroidism

This condition is characterised by weakness, myalgia and the characteristic myxoedema, fatigue, slow movements and delayed reflex relaxation, stiffness. However, muscle disease can also occur in the absence of overt myxoedema. There are two clinical syndromes characteristically described:

(a) Muscle hypertrophy with weakness and painful spasms occurring in adults (Hoffmann syndrome).
(b) Painless muscular enlargement and slow movements have been observed in cretins. The features of this syndrome include retarded intellectual, physical and osseous development, a peculiar facies and generalised muscle hypertrophy (Kocher-Debré-Sémélaigne syndrome) [13, 14]. Myopathy of hypothyroidism is manifested therefore by lower-extremity or generalised muscular hypertrophy, myxoedema and short stature. Occasionally, hypothyroidism may produce proximal weakness and atrophy. Serum creatine kinase is elevated in almost all hypothyroid patients, whether or not other evidence of muscle disease is present. EMG may be normal and demonstrates that the spasms are not manifestations of myotonia. Fibrillation and fasciculation are unusual, unless there is a coincident neuropathy. Biopsy of hypothyroid muscles shows that the structural changes are usually mild. There may be atrophy, necrosis and hypertrophy of single muscle fibres. Glycogen accumulation is usually found. Histochemical staining for oxidative enzymes in mitochondria may show prominent abnormalities, and at the ultrastructural level, mitochondrial swelling and inclusions have been found as well as lipoid granules. In the Kocher syndrome, type 1 atrophy and abnormalities of oxidative enzymes were prominent [13]. Congenital and neonatal hypothyroidism can be detected early by neonatal screening test and corrected otherwise gives craniostenosis and developmental delay.

Metabolic Changes in Hypothyroidism Hypothyroidism reduces protein synthesis. There is a decreased metabolic rate and oxygen consumption as a result of decreased mitochondrial oxidation capacity [6]. Muscle glycogenolysis is impaired, resulting in impaired ischaemic lactate production. The acid maltase level is decreased [15]. The impaired glycogenolysis may contribute to muscle cramps and fatigability. Reduced protein degradation is associated with decreased lysosomal protease activity, both of which normalise with thyroid replacement.

11.2 Steroid Myopathy

Steroid myopathy may be endogenous or iatrogenic. The onset of weakness is usually insidious, starting in the proximal muscles of the legs and arms. Myalgia may accompany the weakness. The levels of serum lactate dehydrogenase, aspartate aminotransferase, creatine kinase and aldolase are usually normal. Patients suffering from steroid myopathy usually have other clinical signs of glucocorticoid excess. The diagnosis of steroid myopathy is simple when significant muscle weakness occurs in a patient receiving steroids for a condition unrelated to the musculoskeletal system. The differentiation of steroid myopathy from an inflammatory myopathy is more difficult. The following criteria can be used: steroid myopathy takes time to develop and weakness that occurs at the onset of a steroid treatment in polymyositis is probably still related to the inflammatory process. If the relevant serum enzymes are elevated, the weakness is probably not steroid induced. Among patients with steroid myopathy, there is a wide range in dose and duration of steroid

treatment received. Patients who have received steroids for less than 4 weeks rarely develop steroid myopathy. Women are twice as likely as men to develop steroid myopathy with the same glucocorticoid dose. Lowering the steroid dose will usually correct the weakness. On EMG needle insertion, activity is normal and the motor unit potentials are of low amplitude and short duration [16]. Although many commonly used steroids can cause myopathy, the fluorinated steroids such as dexamethasone, betamethasone and triamcinolone are more likely to produce muscle weakness [16].

Myopathology Histological studies in either iatrogenic steroid myopathy or Cushing's disease [17] show a selective type 2 fibre atrophy. The biopsy shows atrophic type 2 fibres staining darkly for myofibrillar ATPase. Sometimes the atrophy is so intense that it can resemble a neurogenic atrophy, except that other features of neurogenic disorders ('targets' or 'type grouping') are absent. Lipid droplets are frequently seen in type 1 fibres and electron microscopy shows mitochondrial aggregates and vacuolisation.

11.2.1 Myopathy Due to Excess of Adrenocorticotropic Hormone (ACTH)

Prineas and colleagues [18], in a review of 17 patients who had been treated for Cushing's syndrome by adrenalectomy between 6 months and 14 years previously, observed the association in six patients between the appearance of pigmentation and the occurrence of myopathy. These workers therefore suggested that an extra-adrenal action of ACTH might be a factor predisposing these patients to myopathy. All six patients developed weakness more than 1 year after adrenalectomy, and all were receiving glucocorticoid replacement treatment (hydrocortisone 20–40 mg/d). These patients had proximal muscle weakness and atrophy, but other features differed from those seen in typical steroid myopathy; for instance, four patients exhibited sharp waves and fibrillation on EMG, and in three patients the muscle biopsy showed marked subsarcolemmal lipid deposit. Similar changes can be provoked by ectopically produced ACTH. In muscle, the early changes include the accumulation of subsarcolemmal mitochondria. Many regenerating muscle fibres showed unusual aggregation of filaments, deranged Z disc with filaments attached and T system with tubular networks.

11.3 Drug-Related Myopathies (Table 11.2)

11.3.1 Valproate Toxicity

Children with epileptic seizures treated with valproate may present fatal hepatotoxicity and hyperammonaemia with a syndrome similar to Reye's syndrome [19]. The valproate-induced Reye's syndrome is determined by energy deprivation. Valproate conjugates with carnitine to form valproyl-carnitine, which is preferentially excreted

Table 11.2 Toxic myopathies

Agent	Effects
Valproate	Hepatotoxicity
	Hyperammonaemia
Heroin	Myonecrosis
	Myoglobinuria
Clofibrate	Myonecrosis
	Myoglobinuria
Chloroquine	Increased autophagic mechanisms
Emetine	
Colchicine	

in the urine, and this process may lead to low plasma carnitine. Lowered levels of free carnitine and high levels of short-chain and long-chain acyl-carnitines in plasma have been observed by us after a load of valproic acid in adults and children.

11.3.2 Rhabdomyolysis Caused by Opioids and Clofibrate

The occurrence of acute rhabdomyolysis as a complication of the i.v. injection of heroin was first reported by Richter and colleagues [20]. It is possible that adulteration of the heroin mixtures was responsible. They described four young men presenting severe generalised muscle oedema and weakness, within hours after administration of the heroin preparation. Muscle biopsy showed necrosis of muscle fibres with severe oedema. Creatine kinase and other serum enzymes were elevated and there was gross myoglobinuria. Since this first report, numerous other observations have followed. Clofibrate (Atromid-S) is a branched fatty acid ester used therapeutically as a hypolipidaemic agent. A toxic syndrome characterised by severe muscle pain, cramps and weakness has been described. Tenderness of muscle was accompanied by an elevation of serum transaminases and creatine kinase [21]. The clinician should be aware that the use of clofibrate may cause a severe sense of exhaustion, due to its toxic effect on muscle.

11.3.3 Chloroquine, Emetine, Vincristine and Colchicine

These drugs may cause a severe reversible myopathy. They have a direct effect on mitochondria and result in type 1 fibre atrophy and a vacuolar myopathy by stimulating autophagic mechanisms. Whisnant and colleagues [22] reported the development of widespread muscular weakness in four patients requiring long-term chloroquine treatment of collagen vascular diseases. Biopsies showed vacuolar myopathy. Itabashi and Koykmen [23] observed a reversible granulo-vacuolar myopathy in a 46-year-old woman with abdominal sarcoidosis after 9 months of treatment with chloroquine. McDonald and Engel [24], in a study of experimental chloroquine myopathy, found vacuolisation and frequent splitting of muscle fibres,

proliferation of membrane systems and abundance of myeloid bodies reactive for acid phosphatase. They observed the formation of diffuse autophagic vacuoles in muscle, somewhat similar to those observed in type 2 glycogenosis. Red muscle, composed of type 1 fibres, is more affected than white muscle (type 2 fibres). Colchicine arrests mitotic division and has been used for centuries for the treatment of gout. Its neuromuscular toxicity in man is largely unrecognised. Kunge and colleagues [25] reported 12 cases of colchicine myopathy and neuropathy: they present with elevation of serum creatine kinase and a mild axonal polyneuropathy. EMG shows myotonic changes in proximal limb muscles. Biopsy demonstrates vacuolar myopathy with marked accumulation of lysosomes and autophagic vacuoles. The pathogenesis may involve the disruption of a microtubule-dependent cytoskeletal network that interacts with lysosomes. Necrotic muscle fibres and large complex membranous bodies were seen in rabbits by D'Agostino [26] in experimental colchicine myopathy.

Emetine, a constituent of ipecac, has been used as an amoebicidal agent. An adverse aspect of its use is weakness, pain, tenderness and stiffness of muscles. Duane and Engel [27] found that emetine administered to rats produces myofibrillar degeneration, necrosis and regeneration. The soleus muscle seems to be more affected than the gastrocnemius muscle. Myofibrillar degeneration was observed in areas of mitochondrial loss. Vincristine, an alkaloid used in leukaemia, is a well-recognised cause of peripheral neuropathy. However, there is also a direct effect on muscle. Anderson and colleagues [28] and Clarke and colleagues [29] have studied its effect in an experimental model and have demonstrated that vincristine may cause spheromembranous degeneration, suggesting that vincristine toxicity impairs the biodegradation of muscle phospholipids.

11.4 Nutritional and Secondary Deficiency States

Carnitine deficiency may be seen in cirrhosis [30], in pregnancy [31], during total parenteral nutrition in infants and in some adults [32] undergoing surgery. In these patients, inadequate exogenous supplement, hormonal factors and defective endogenous synthesis contribute to the carnitine-deficient state. The low carnitine content in infant liver may explain the steatosis observed in infants on total parenteral nutrition and suggests an essential role during early stages of human life, when endogenous synthesis and storage are probably not adequate. Similar observations apply to the plasma carnitine deficiency found in undernourished populations with schistosomiasis worm infection [33].

11.4.1 Carnitine Changes in Various Metabolic Slates: Fasting, Diabetes

In fasting man, the increase in plasma long-chain acyl-carnitines parallels that of plasma free fatty acids [34], reflecting the conversion of increased fatty acids first to

acyl-CoA and then to carnitine derivates in many tissues. A similar marked increase in serum acyl-carnitines and decreased free carnitine was observed by Genuth [35] in diabetic ketoacidosis. He reported that insulin reverses this pattern towards normal. Plasma insulin levels decline in fasting subjects [34], accompanied by a qualitative redistribution of plasma carnitine fractions while refeeding restores the plasma carnitine fractions to normal, as plasma insulin rises. It therefore appears that the increased ratio of acyl-carnitines to free carnitine may be related to reduced secretion of insulin, a modulator which might negatively influence fatty acid oxidation in tissues [36]. Genuth [36] has observed that a high plasma glucagon concentration causes a decrease in total plasma carnitine, particularly of the free carnitine fraction. McGarry and colleagues [37] demonstrated that the liver carnitine concentration increases following glucagon administration. The hormonal variations that occur in patients undergoing chronic haemodialysis are similar to those found in diabetes or fasting subjects. Hyperglucagonaemia has been observed in haemodialysed patients [38, 39]. Furthermore, a decreased peripheral tissue sensitivity to insulin in uraemic patients is a well-known feature, since these patients have a normal or increased secretion of insulin [40, 41].

11.4.2 Myopathies Caused by Nutritional Deficiency (Table 11.3)

It has been known for many years that deficiencies of vitamins E and D can cause myopathy [42]. The vitamin B deficiencies do not affect muscle, although they cause profound central and peripheral nervous system changes. Deficiency of vitamin B_t (carnitine) may result in a lipid storage myopathy. Protein-energy malnutrition, which causes Kwashiorkor in infants and children, can produce secondary carnitine deficiency but is not associated with overt pathological changes in muscle. The only mineral nutritional deficiencies described in association with myopathy are those of selenium and possibly magnesium [43, 44].

11.4.3 Vitamin E Deficiency

Lesions in muscle are produced in animals by a diet deficient in vitamin E. In rabbits, the deficiency results in muscle necrosis. The necrotic fibres are invaded by

Table 11.3 Myopathies caused by nutritional deficiency

Compound	Effect
Vitamin E (alpha-tocopherol)	High CK, neuromyopathy
Vitamin B_t (carnitine)	Protein-energy malnutrition
Selenium	Myopathy
Magnesium	
Iron	Anaemia, myeloneuropathy
Copper	

macrophages and polymorphonuclear leucocytes. Elevated serum creatine kinase is observed [45] and returns to normal on reintroduction of vitamin E, when regeneration of muscle fibre occurs. That vitamin E deficiency can cause a primary muscle disease in man has, however, not been fully established. Thomasi [46] reported the case of a patient who developed jaundice and pruritus in infancy because of biliary atresia; he was treated with high doses of cholestyramine and had a reduced plasma vitamin E level. At 7 years, the patient had severe generalised muscle weakness with high serum creatine kinase. Muscle biopsy disclosed angulated fibres. The patient improved after 4 months of treatment with massive doses of vitamin E. Muscle strength and plasma level of alpha-tocopherol returned to normal. Vitamin E deficiency following fat malabsorption can cause a spinocerebellar type of syndrome with neuropathy, muscle inclusions, retinal degeneration and ophthalmoplegia [47]. A case of Friedreich's disease with normal fat absorption and low plasma vitamin E has been reported by Stumpf and colleagues [48]. However, refeeding vitamin E did not improve the neurological picture.

11.4.4 Iron and Copper Deficiency

Given their similar physiochemical properties, whole-body iron and copper homeostasis is linked to dietary and copper absorption in the upper small bowel. Perhaps, the first detailed description of iron-copper interactions in humans dates back to the mid-1800 in Italy and France. Young women suffered from a disease called chlorosis with pale complexion, amenorrhea and lethargy. It is also conceivable that these young women suffered from copper deficiency. Iron assimilation from the diet must be tightly controlled. In fact, there are mechanisms that induce transactivation of gene in erythrocytes by an hypoxia-inducible factor (HIF2alpha) by iron deprivation. Lack of iron decreases haemoglobin production which impairs oxygen delivery to several tissues leading to hypoxia. Several genes encoding iron transport-related proteins are upregulated by the transcriptional mechanism involving HIF2alpha. Molecular mediators governing iron-copper interaction and total body stores are described by Gulec and Collins [49]. Several questions and foci for future research remains unanswered, for instance, what is the biological significance of increased copper levels in enterocytes during iron deficiency and why does copper deficiency cause anaemia.

Copper deficiency is an under-recognised cause of myeloneuropathy. Damage to mitochondria and alteration of several copper transport proteins was documented in muscle by Spinazzi and colleagues [50]. Usually, copper deficiency might be easily missed [51], but it causes a neurological dysfunction, practically indistinguishable from subacute combined degeneration. Copper deficiency is an under-recognised cause of cytopenias and myeloneuropathy; the neurological sequelae of copper deficiency can become debilitating and irreversible making early recognition an important point. Risk factors of copper deficiency appear to be upper gastrointestinal tract surgery, bariatric surgery, zinc overload, ingestion of zinc-containing dental fixative and malabsorption syndrome. Laboratory indicators of copper deficiency include

cytopenia and low copper. In clinical practice, guidelines recommended testing for copper deficiency in post-bariatric surgery patients and anaemia, neutropenia and myeloneuropathy. Spinal cord magnetic resonance imaging is abnormal in half the patients, and neurophysiological studies might show axonal sensorimotor polyneuropathy. The reversibility of the condition depends on the stage of neuronal deficiency.

Highlights

- Thyroid action is important to maintain metabolism in muscle; often insidious hypothyroidism can be caused by Hashimoto autoimmune disease or thyroid removal.
- Steroids action is particularly evident in type 2 fibres in muscle biopsy; fluorinated steroids should be avoided in treating inflammatory muscle disease.
- Malabsorption syndrome can cause secondary carnitine deficiency, iron and vitamin B deficiency.
- Copper deficiency is an under-recognised cause of cytopenia and myeloneuropathy.
- Clinicians should have a low threshold for measuring thyroid serum iron and copper in patients with unexplained proximal muscle weakness in the context of previous surgical procedures or malabsorption.

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Vitamin D Deficiency in Muscle

12

Hussam Abou Al-Shaar and Saeed A. Bohlega

12.1 Epidemiology of Vitamin D Deficiency

Vitamin D deficiency is an extremely common condition, especially in the elderly. It is estimated that more than 60 % of nursing home residents in the US are vitamin D deficient [1]. However, vitamin D deficiency can be present among young and healthy individuals as well. According to the National Health and Nutrition Examination Survey (NHANES) of 2877 US children and adolescents, it is estimated that 10.3 % of them had insufficient vitamin D levels (12–20 ng/mL), and 4.6 % had vitamin D deficiency (<12 ng/mL) [2].

These results are comparative to those encountered among Canadian and European populations [3]. Interestingly, the prevalence of vitamin D deficiency is drastically higher in the Middle Eastern countries, which might be attributed to their cultural and religious practices [4]. Moreover, it has been noted that vitamin D deficiency is more common among women and dark-skinned people, as the excess melanin interferes with the cutaneous synthesis of vitamin D [5].

12.2 Biochemistry of Vitamin D

Vitamin D is a fat-soluble steroid hormone synthesized in the skin or found in dietary sources. There are two forms of vitamin D: vitamin D2 (ergocalciferol) derived from plants and vitamin D3 (cholecalciferol) derived from animals or synthesized in the epidermis layer of the skin from 7-dehydrocholesterol conversion in response to

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ultraviolet light (UVB). Both forms are transported to the liver via vitamin D-binding protein in order to undergo their first hydroxylation process by 25-hydroxylase enzyme, which gives rise to *25-hydroxycholecalciferol*. 25-hydroxycholecalciferol undergoes another hydroxylation (rate-limiting step) mainly in the proximal tubules of the kidney by 1-α-hydroxylase enzyme giving rise to 1,25-dihydroxyvitamin D2 and 1,25-dihydroxyvitamin D3 (*calcitriol*), respectively [6, 7].

It is the action of calcitriol on vitamin D receptors (VDR) in target tissues that produces the desired effects of vitamin D. Calcitriol binds to VDR inducing conformational changes within it, allowing it to heterodimerize with the retinoid X receptor (RXR). This complex binds specific genomic sequences known as vitamin D response elements (VDREs) in order to influence gene transcription and produce its desired effects [8]. It has been shown that this binding site is located near autoimmune and cancer-associated genes, which might explain the higher tendency of *autoimmune diseases* and cancers among vitamin D-deficient individuals [8]. However, the effects of vitamin D are not entirely "genomic." Vitamin D plays an essential role in MHC class I assembly, molecular chaperoning, and others through its nonnuclear effects on VDR [7, 9].

The 24-hydroxylase (CYP24A1) enzyme, which is found in nearly all tissues of the body, especially the kidneys, limits the amount and catabolizes calcitriol in target tissues by converting it to inactive metabolites, including 1,24,25-hydroxycholecalciferol and calcitroic acid [7].

12.3 Causes of Vitamin D Deficiency

Vitamin D deficiency can happen due to various etiological factors. Anything that might interrupt its synthesis can yield to deficiency [10]. Some of the causes include:

- Inadequate exposure to sunlight
- Malabsorption (e.g., celiac disease)
- *Liver diseases* (e.g., cirrhosis)
- *Renal disease* (e.g., renal failure)
- Medication that induce p450 enzymes in the liver accelerating vitamin D metabolism (e.g., phenytoin, rifampicin)
- Steroids
- Pregnancy
- Season and latitude
- Exclusively breast milk-fed children, as it carries minimal amounts of vitamin D

12.4 Effects of Vitamin D on Muscles and Nervous System

The effects of vitamin D are not limited to *calcium* and *phosphate* homeostasis and *bone health*. There is increasing evidence supporting the role of vitamin D in the nervous system and muscle function. It has been shown that muscles and numerous

areas within the central nervous system harbor VDR including the pituitary gland, forebrain, hindbrain, and spinal cord [11]. In addition, 1-α-hydroxylase enzymes have been detected in the brain; and some of the vitamin D metabolites have been retrieved from the cerebrospinal fluid [12].

In the nervous system, vitamin D promotes neural differentiation, growth, and maturation. It also protects the nervous system from toxicity and decreases the rate of neurological injury. This effect has been noted by the increased rate of multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis, and Alzheimer's among vitamin D-deficient individuals. In addition, vitamin D and its metabolites contribute to the synthesis of some neurotransmitters including serotonin, dopamine, acetylcholine, and catecholamines. Its role in neuroplasticity is crucial as it stabilizes the cellular structures and maintains the mitochondrial functions [13].

Grossly, vitamin D-deficient animals demonstrated increased overall brain size and hemispheric length, cortical layer thinning, and big lateral ventricles [14]. Histologically, deficient animals showed increased cellular proliferation, higher rates of mitosis, and reduced cellular apoptosis [15].

As in the nervous system, vitamin D stimulates *mitogen-activated protein kinases (MAPK)* family in myoblasts, increasing the expression of genes responsible for cellular proliferation and differentiation [16]. It has also been shown to have a role in the regulation of the contractile elements, cytoskeleton, and phospholipid membranes [17, 18].

On muscle histology, vitamin D-deficient individuals display nonspecific findings, which include atrophy of type II (fast twitch) muscle fibers, fatty infiltration, presence of glycogen granules, and fibrosis. In addition, degenerative changes on electron microscopy with small foci of fiber necrosis, Z-band degeneration, and lytic vacuoles have been noted [19, 20].

12.5 Myopathy and Myalgia

As we described before, the effects of vitamin D are beyond calcium and phosphate homeostasis and bone health. Vitamin D deficiency is implicated in many neuromuscular diseases.

Muscle weakness (*myopathy*), muscle pain (*myalgia*), bone pain, and hypotonia are commonly encountered among patients with vitamin D deficiency (e.g., *rickets* and *osteomalacia*). The muscle weakness noted in vitamin D deficiency is progressive and mostly in the proximal musculature [21, 22]. This muscle weakness will lead to difficulty rising from a seated position (Gower's sign), climbing stairs, or lifting objects. In addition, it may lead to changes in gait (e.g., waddling and reluctant gait) as well as imbalance [22, 23]. It is important to note that it is sometimes difficult to distinguish between the giving away weakness due to bony pain and the muscle weakness encountered in vitamin D deficiency. In vitamin D deficiency, the muscles are not painful and tender to move. Chronic cases of vitamin D deficiency might develop skeletal abnormalities like bowing and pathological fractures.

The pathogenesis of the myopathy and myalgia remains elusive. However, low calcium, phosphate, and calcitriol along with high parathyroid hormone have been attributed to the development of these symptoms [24]. The myopathy and myalgia encountered in these conditions respond rapidly to high vitamin D therapy [23–25].

However, it is important to note that the pattern of muscular weakness among vitamin D-deficient individuals is not specific and is commonly encountered among other endocrine disorders like Cushing's syndrome and hyperthyroidism [22]. In addition, vitamin D-deficient individuals with muscle weakness demonstrate electromyographic changes reflecting myopathy, but without specific topographies [26].

12.6 Myotonic Dystrophy

Myotonic dystrophies type 1 and type 2 are a group of autosomal dominant-inherited disorders characterized by the presence of early-onset cataract, myotonia, and muscle weakness and atrophy [27]. Vitamin D levels among patients with myotonic dystrophies are generally low. Interestingly, 18 % of patients with myotonic dystrophy type 1 have a concurrent hyperparathyroidism, and the severity of their disease correlates with the parathyroid hormone level [28]. Patients with myotonic dystrophy type 2 are commonly known to have high parathyroid hormone level. However, its exact prevalence has not yet been established. In addition, it has been demonstrated that a positive correlation between *CTG repeats* and parathyroid hormone levels exists among myotonic dystrophy type 1 patients [28, 29].

Vitamin D deficiency among myotonic dystrophy type 1 patients has been attributed to insufficient cutaneous synthesis, altered gastrointestinal absorption, or abnormal hepatic hydroxylation. However, studies have shown that patients given oral cholecalciferol showed a normal increase of circulating vitamin D levels, ruling out malabsorption and liver dysfunction. Thus, impaired cutaneous synthesis remains the main acceptable mechanism of vitamin D deficiency, as skin changes (e.g., baldness and skin tumors) are common in such patients [27, 30]. The relation between vitamin D deficiency and myotonic dystrophies remains elusive. It is yet to be discovered whether the deficiency has a causal relationship with the development of these diseases or is the result of the disease course and hyperparathyroidism.

12.7 Myasthenia Gravis

Myasthenia gravis is an autoimmune disease resulting from the formation of autoantibodies against the postsynaptic acetylcholine nicotinic receptors. The association between vitamin D deficiency and myasthenia gravis is not entirely understood. Recent research fails to demonstrate clear associations between the two. However, a recent study showed that vitamin D supplementation in myasthenia gravis improved the symptoms in the majority of patients as reflected by a reduction in the myasthenia gravis composite scale score [31]. It is thought that these effects are

mediated by regulating the autoimmune process involved in myasthenia gravis and by maintaining and stimulating muscle function through the effects of vitamin D on the muscles' VDR [31, 32].

12.8 Drug-Induced Myopathy

According to the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (*SEARCH*) collaborative group's trial, myopathy can be either incipient or definite. Incipient myopathy is defined by a CK level >3 times the upper normal limit and >5 times the patient's baseline in addition to an alanine aminotransferase (ALT) level >1–7 times the baseline. Definite myopathy is defined as a CK level ≥10 times the upper normal limit plus unexplained muscle pains. Rhabdomyolysis is defined by a CK level ≥10 times the upper normal limit plus evidence of end-organ damage (elevated serum creatinine). The presence of myoglobinuria and electrolyte abnormalities supports the diagnosis of *rhabdomyolysis* [33].

The myopathy encountered during statin therapy ranges from simple myalgia to life-threatening rhabdomyolysis [34]. The risk of myopathy is mainly attributed to the drug dosage with the more lipophilic statins (e.g., *simvastatin*) having the highest risk [35]. Other factors that play a role in the development of statin-related myopathy include old age (>80 years), Asian ethnicity, female gender, low body mass index, frailty, and having concurrent systemic diseases (e.g., diabetes mellitus, hypothyroidism, renal or hepatic disease) [36]. The development of myalgia among these patients is an indication of drug intolerance [37]. Vitamin D deficiency significantly augments the myopathy among patients on statin therapy. Therefore, cessation of statin therapy in conjunction with high-dose vitamin D supplementation in those patients results in the resolution of symptoms in the majority of patients [7].

Various other medications can cause myopathy and myalgia, either as a side effect or due to increased vitamin D metabolism. Antiepileptic medications (phenytoin), antibiotics (rifampicin), and other drugs have been shown to induce liver p450 enzymes increasing the catabolism of vitamin D, resulting in a picture similar to vitamin D-deficient myopathy [10].

12.9 Treatment and Complications

Vitamin D supplementation can help in treating and preventing the development of neuromuscular symptoms. These symptoms tend to increase the risk of *falls*, *fractures*, injuries, and affect the *quality of life*, especially in the elderly. It has been estimated that 30 % of community-dwelling people over the age of 65 suffer from repeated falls each year, 20 % of which require medical attention [38, 39]. Vitamin D supplementation in conjunction with calcium has been shown to be effective in the prevention of falls and improvement of the neuromuscular functions among the elderly. Therefore, it was recommended to give vitamin D supplementation and

calcium for people over 65 years [7]. In addition, vitamin D supplementation should be given to all patients with neuromuscular conditions to prevent the development of these undesirable complications.

It is recommended to give 200 IU/d of vitamin D for children and adults up to the age of 50 years, 400 IU/d for adults from the age of 50–70 years, and 600 IU/d for those older than 70 years [40]. It has been noted that daily supplements of ≥800 IU/d vitamin D plus calcium has the potential to reduce vertebral and nonvertebral fractures in up to 26 % among the elderly [41, 42]. Alternatively, given 100,000 IU oral vitamin D every 4 months is equally effective [43].

The *complications* of vitamin D therapy (*hypervitaminosis D*) are minimal and related to very high doses. Vitamin D toxicity can cause high calcium levels (hypercalcemia), which can lead to kidney stones, bone loss, and organ calcification (e.g., heart and kidneys). However, the toxicity is very unlikely in healthy individuals at intake levels lower than 10,000 IU/day [40, 44].

Conclusions

It is clear that vitamin D plays an essential role beyond calcium and phosphate homeostasis and bone health. Vitamin D deficiency is common in patients with neuromuscular diseases. *Screening* patients with these disorders for deficiency is essential, as early detection and intervention might help prevent the development of symptoms and improve the quality of life in these patients. Patients with neuromuscular conditions must receive vitamin D *supplementation*, once diagnosis is established. It is yet to be discovered whether vitamin D deficiency plays a role in the development of these diseases or is just a result of the poor nutrition and limited sun exposure commonly encountered in such patients. Future research is needed to delineate this association and to answer these questions and more.

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Intensive Care Unit-Acquired Weakness 13

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13.1 Introduction

Intensive care unit-acquired weakness (ICUAW) is a severe acquired muscle weakness during critical illness and for which there is no other explanation than the critical illness itself [1]. The condition delays rehabilitation and may not be completely reversible. The acute outcome and long-term functional outcome are strongly dependent on age, co-morbidities and the length of intensive care unit stay [2].

13.2 Prevalence and Risk Factors

The prevalence of ICUAW is strongly dependent on the type of patient population studied; e.g. ICUAW occurs more frequently in patients with longer exposure to mechanical ventilation: 33 % of patients mechanically ventilated up to 5 days and 43 % of patients mechanically ventilated up to or more than 7 days develop ICUAW [3], while the frequency rises to 67 % in patients mechanically ventilated up to or more than 10 days [4]. Several risk factors/triggers in addition to mechanical ventilation have been reported: sepsis, bacteraemia, systemic inflammatory response syndrome, multiorgan failure, muscle unloading, steroid treatment, malnutrition, hyperglycaemia/insulin resistance and neuromuscular blockade [5].

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13.3 Clinical Signs

Symmetrical and flaccid weakness of limb muscles, more pronounced in proximal than distal muscles, and weakness of respiratory muscles, which is responsible for difficulties in weaning from mechanical ventilation, are the main features. Facial and ocular muscles are often spared; tendon reflexes are generally reduced, but may be normal. Sensory loss, if present, is usually localised in distal parts of the limbs and is an argument for CIP, but may be due to other causes, such as diabetes. Autonomic dysfunction may be present [6]. While ICUAW is relatively obvious in patients with a primary non-neurological disorder, it may be difficult to notice in patients with the primary lesion in the central nervous system [7]: affection of the peripheral neuromuscular compartment was considered in patients with primary central nervous system disorders when previously spastic patient developed flaccid weakness and an absence of myotatic reflexes, and weaning from mechanical ventilation could not be achieved.

13.4 Diagnosis

ICUAW may be caused by critical illness myopathy (CIM), critical illness polyneuropathy (CIP) or a combination of both [8].

13.4.1 Manual Muscle Testing

According to the American thoracic society practice guideline for the diagnosis of ICUAW [3] and others [9], the Medical Research Council (MRC) manual muscle testing (MMT) is the recommended diagnostic tool for the identification of ICUAW, due to its universal availability. The lack of a universally accepted and validated "gold standard" and inapplicability of MMT in an uncooperative or sedated patient are major limitations, but a more reliable and *universally* available test for muscle strength has not yet emerged [3]. A semi-quantification of muscle strength by MMT, using a six-point MRC scale, was recently proposed [10]: a summed score <48/60 designates "significant weakness", and a score <36/60 indicates "severe weakness"; three muscle groups in all four limbs are evaluated (arm abduction, elbow flexion, wrist extension, hip flexion, knee extension and ankle dorsiflexion), giving a total score of 60. A simplified version of the MRC scale, consisting of four grades, i.e. 0 = paralysis, 1 = severe weakness (>50 % loss of strength), 2 = slight weakness (<50 % loss of strength) and 3 = normal strength, was developed [11] since MMT using the six-point MRC scale is more time-consuming and discriminating between strength categories at the upper part of the scale is difficult [12]. Although tested on a relatively small number (29) of patients with ICUAW, it has been stated that the simplified version is comparable to the standard MRC scale for the clinical diagnosis of ICUAW [12]. Handgrip dynamometry is an objective outcome measure and can be used as a quick diagnostic test [9], and since it is easily administrated by any

member of the multidisciplinary team, it facilitates early identification of patients who may benefit from therapy [12]. Cut-off scores less than 11 kg in males and less than 7 kg in females indicate significant weakness [12, 13].

13.4.2 Electrophysiological Testing

Electrophysiological testing is usually used in making a diagnosis of ICUAW; concentric needle EMG in 90 % of studies, nerve conduction studies (NCSs) in 84 % of studies and direct muscle stimulation [14] in 19 % of studies [3], but these tools are less universally available in clinical practice; are time-consuming, technically challenging and expensive; and require subspecialists. Nevertheless, electrophysiological tests are minimally invasive, easily reproducible and possibly bedside performed, and the results are available immediately [6]. CIP is an axonal sensorimotor polyneuropathy, which is characterised electrophysiologically by reduced amplitude of sensory nerve action potential (SNAP) and reduced compound motor action potential (CMAP); latency and nerve conduction velocities remain normal or are slightly prolonged; CIM has normal SNAP but, similar to CIP, has reduced CMAP, which is of increased duration [15]. Both CIP and CIM may have abnormal spontaneous activity on needle EMG. The duration of abnormal spontaneous activity is important for differentiation between CIP and CIM – a shorter duration (5–15 days) is an argument for myopathy, since it would need more time to evolve in the case of axonal lesion [7]. If MUPs could be estimated (requires alert and motivated patient), myopathic MUPs and the myopathic recruitment pattern could be detected in CIM [16]. CIP and CIM have some similar electrophysiological characteristics, e.g. a low amplitude of CMAP, which is consistent with functional loss of generators of the compound electrical muscle response, i.e. muscle fibres; this may be brought about by the loss of either axons or muscle fibres [7]. A pattern of recruitment of MUPs and analysis of MUP parameters may help to differentiate between CIP and CIM [7], as well as the duration of CMAP [15] and CMAP on direct muscle stimulation [14]. Unfortunately, direct muscle stimulation is fairly rarely (19 % of studies) used [3]. Nerve conduction studies and EMG cannot always differentiate between CIP and CIM, e.g. in a recent study [17] CIP was detected in 38 % and combined CIP and CIM in 17 %, and 45 % of patients were undetermined. In spite of the limitations, a simplified electrophysiological test has been proposed to be used as a *screening* test for probable CIM/CIP [9, 17]. The peroneal nerve conduction test has been validated in two multicentric studies as a 100 % sensitivity test, compared to complete nerve conduction studies and concentric EMG, in the diagnosis of probable CIM/CIP; no false-negative results were detected, but false-positive results were observed: some patients had peroneal nerve mononeuropathy when analysed by complete nerve conduction studies and EMG, so the specificity of peroneal nerve conduction study was found to be 85 % [17]; it is worth mentioning that patients with diabetes were not included in the study. The peroneal nerve conduction test cannot distinguish between CIP and CIM or combined CIP and CIM, but a suspicion of ICUAW can be confirmed. In addition the test is very

"economic" in terms of time, since it can be performed in 10 min [17] and since it does not require the patient's collaboration, it is a valuable objective method in detecting probable CIP or CIM. A potential useful application of this test could be at the early phase of an ICU stay, when volitional tests are rarely performed, and at the evaluation at ICU/acute hospital discharge – a normal test excludes CIP or CIM and the need for further neurophysiological evaluation, while an abnormal test indicates probable CIP or CIM or some peripheral nerve disorder, such as peroneal nerve mononeuropathy, which should be further evaluated by a neurologist [9].

Since 80 % of subjects with EMG/NCS abnormalities had moderate to severe muscle weakness [3], correlation between electrophysiological studies and clinically detected muscle weakness is considered good. However, most studies used MMT and electrophysiological tests sequentially, not comparing two diagnostic approaches; in spite of this, electrophysiology has aided our understanding of the mechanisms of ICUAW and can aid in determining a patient's ability to respond to certain treatments and should probably not be secondary to MMT (or any diagnostic approach) [3]. Electrophysiological alterations can be detected earlier than the clinical signs and have predictive power: e.g. a reduction of the amplitude of CMAP can precede ICUAW for 48 h in patients with sepsis [18]. Electrophysiological tests are also important with respect to acute outcome: hospital mortality is higher in patients with abnormal NCS/EMG than in those with normal findings [9].

The prevalence of electrophysiological abnormalities in ICU patients is strongly dependent on the population of patients enrolled: it varies from 46 % [1] to 76 % [9], if mostly patients with sepsis, multiorgan failure and prolonged mechanical ventilation are recruited.

Muscle biopsy and nerve biopsy are used infrequently for the diagnosis of CIM/CIP, in 26 and 6 % of studies [3].

13.4.3 Muscle Biopsy

On cryostat sections of muscle biopsy obtained 24 h after the onset of symptoms, slight structural abnormalities are present as smudgy purplish staining of muscle fibres with modified trichrome stain [19]. Myofibrillar ATP-ase activity may be reduced (Fig. 13.1a), but immunostaining for myosin heavy chains does not show attenuation or attenuation is minimal. On late biopsies (1–2/3 weeks after the onset of symptoms), histochemical activity of cytochrome–oxidase may be reduced (Fig. 13.1c) and activity of acid phosphatase increased (Fig. 13.1e). Necrotic muscle fibres (Fig. 13.2a), as well as scattered atrophic angular fibres or small group atrophy, may be present (Fig. 13.2b). By electron microscopy on longitudinal view, loss of myosin filaments is observed (Fig. 13.3). Electrophoresis of total muscle homogenate detects a reduction of myosin in relation to actin [20] (Fig. 13.4). There is no predilection for the loss of the specific myosin heavy chain isoform [21] but more severe muscle atrophy is usually observed in fast fibres. No inflammatory changes are detected in CIM [22]. Increased macrophages in endomysium may be found.

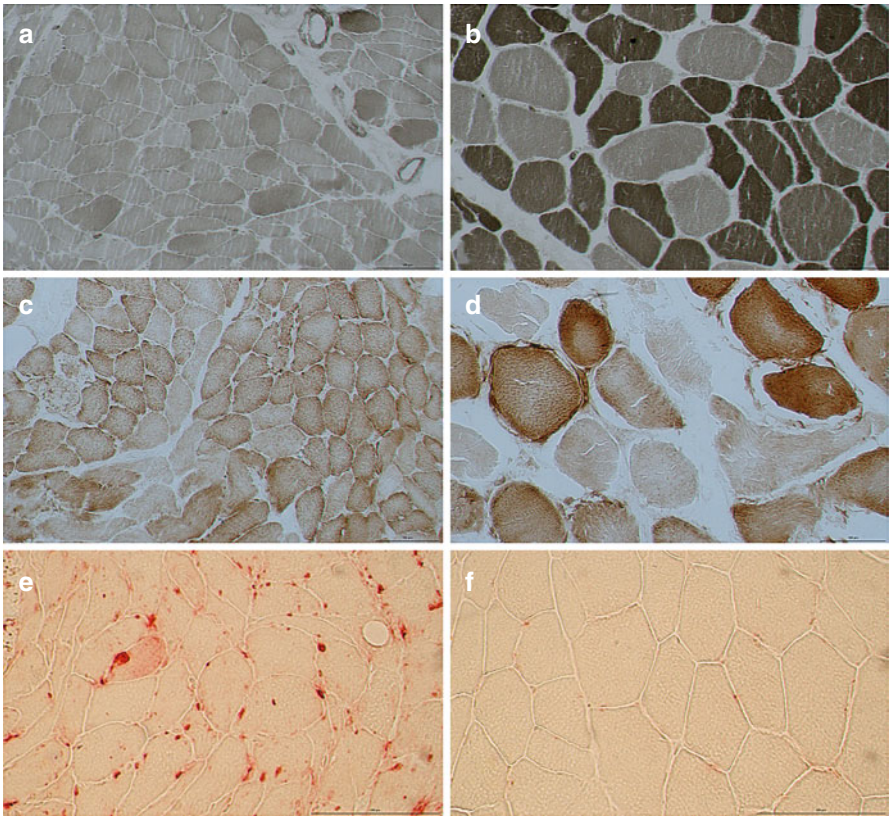

Fig. 13.1 Histochemical demonstration of myofibrillar ATP-ase activity pH 9.4 (**a**), cytochrome–oxidase (**c**) and acid phosphatase (**e**) in CIM compared to control (**b**, **d**, **f**). Enzyme activities of myofibrillar ATP-ase and cytochrome–oxidase are reduced; acid phosphatase activity is increased below the sarcolemma and in the endomysium. Cytochrome–oxidase activity is nearly absent in necrotic fibres. Muscle biopsy of the vastus lateralis muscle in a 59-year-old female patient with CIM (**a**, **c**) and in a 74-year-old female patient with CIM (**e**). Bar 100 µm

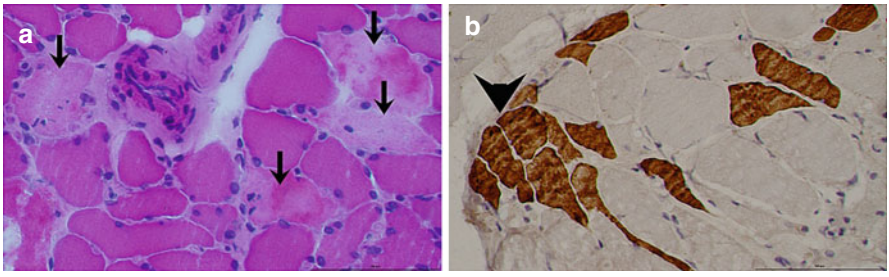

Fig. 13.2 General histopathology of CIM. Haematoxylin–eosin (**a**) and myosin heavy chain 2A (**b**). Necrotic fibres are marked by *arrows* (**a**). Small group atrophy (*arrowhead*) and scattered atrophic fibres mostly of type 2A fast fibres (**b**). (**a**) The same patient as shown in Figs. 13.1a, c and (**b**) the same patient as shown in Fig. 13.1e. Bar 100 µm

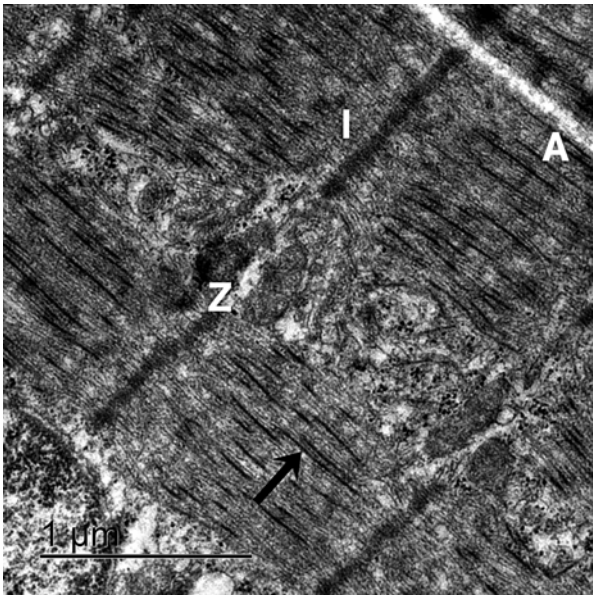

Fig. 13.3 Electron microscopy shows severe loss of myosin filaments (*arrow*) which causes nearly disappearance of *A* band. Actin filaments are preserved and *I* band and *Z* line look normal. The same patient as shown in Fig. 13.1a, c

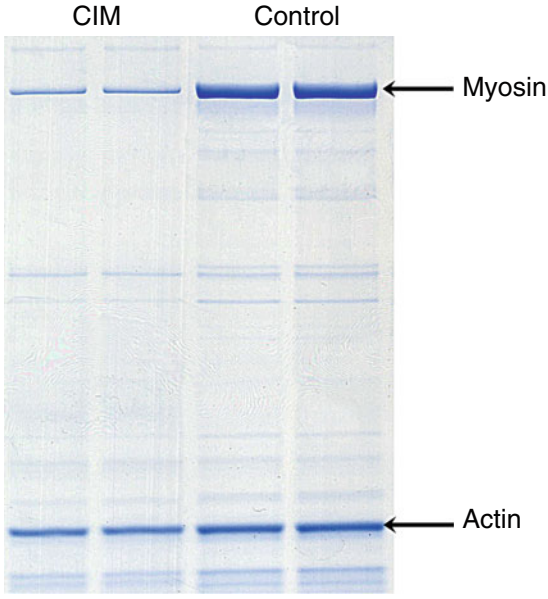

Fig. 13.4 Electrophoresis of total muscle homogenate. Severe loss of myosin in relation to actin. The same patient as shown in Fig. 13.3

Possible "neuropathic elements" can be observed in addition, e.g. small group atrophy or scattered angular fibres (Fig. 13.2b) or even fibre-type grouping; they may reflect a pre-existing chronic condition such as axonal neuropathy (small group atrophy) due to diabetes or previous reinnervation due to radiculopathy (fibre-type grouping) or may be related to distal concomitant axonal damage (scattered angular fibres), if CIM and CIP coexist. Since no reliable marker of acute denervation exists, it is impossible to state whether the scattered angular fibres result from acute denervation (i.e. acute neuropathy) or from chronic neuropathy.

Acute necrotising myopathy of ICU is diagnosed, if necrotic fibres are the outstanding feature; necrotic fibres may be related to concomitant toxic myopathy, due to adverse effect of pharmacotherapy, or muscle fibre necrosis may be considered as an advance stage of CIM; acute necrotising myopathy of ICU is often associated with myoglobinuria [22].

Muscle biopsy is useful for the demonstration of characteristic myosin loss and is important with respect to prognosis, since CIM has more favourable short- and long-term outcomes than CIP [23]. An exception is the prognosis for recovery from weakness of acute necrotising myopathy of ICU, which is very poor [22].

Muscle biopsy is not universally available, is invasive and time-consuming. In addition unspecific, mixed myopathic–neuropathic changes may be detected and caution in the interpretation is needed, since neuropathic signs can be chronic, not related to ICUAW. Morphological analysis also takes time and is fairly inconvenient for the demands of an intensive care. Quantification of the myosin/actin ratio in electrophoresis is more appropriate with respect to time, since it can be performed in 1 or 2 days, but further studies are needed in this field to understand the clinical significance of different degrees of myosin loss.

13.4.4 Nerve Biopsy

Nerve histology is initially preserved. Most sensory nerves in early biopsies (day 15 of sepsis) look normal, despite having reduced SNAP [8]. Late biopsies (day 56) demonstrate axonal loss [8], but this is an unspecific change. Axonal loss observed in biopsies of sensory nerves refers to large axonal loss. Small fibre neuropathy was recently demonstrated in skin biopsies of the critically ill [24]. Small fibre neuropathy may be responsible for neuropathic pain, stocking and glove sensory loss, cool extremities and burning pain in the survivors of CIP [6].

Axonal degeneration was also observed in autopsy samples of sympathetic chain and vagal nerve [25], and autonomic dysfunction is frequently observed in the critically ill [6].

13.5 Pathophysiology

CIM and CIP are not isolated events but an integral part of multiorgan dysfunction syndrome in severe illness and a shared pathogenesis for CIM and CIP is likely [2]. A review of proposed pathophysiological mechanisms from clinical studies and animal experiments was recently published [5].

13.5.1 CIM

Skeletal muscle dysfunction in CIM is a combination of reduced muscle mass (muscle atrophy) and impaired contractility [2]. A specific pathomorphological lesion in CIM is early selective loss of myosin myofilaments relative to actin [20, 26]; however myopathies in pure sepsis do not produce severe myosin loss [5]; the same authors [5] proposed that myopathy in pure sepsis should be considered as a subtype of ICUAW, in addition to CIP and CIM, but at present this is still under consideration.

13.5.1.1 Muscle Atrophy

In the critically ill, several processes, such as inactivity, unloading, immobility, inflammation, cellular energy stress or food deprivation, can cause muscle atrophy [2]. Muscle atrophy may contribute to weakness, premature fatigue and glucose intolerance [27]. Muscle atrophy in CIM is the result of increased muscle proteolysis and diminished protein synthesis. The ubiquitin–proteasome system (UPS), studied mostly in patients with sepsis [28, 29], and calpain activation [21, 30, 31] mediate enhanced proteolysis in the critically ill. The role of the caspase family of cysteine proteases in muscle proteolysis in the critically ill is suggested from animal studies [5]. Lysosomal proteases, cathepsins, have been evaluated for their contribution to muscle loss in sepsis [32], but there is no current consensus on the role of cathepsins in CIM [5]. Increased lysosomal (and proteasomal) activation was observed in the diaphragm of prolonged (15–276 h) mechanically ventilated patients [33], and it was concluded that activation of both systems is responsible for fibre atrophy in the critically ill. However, in adult *prolonged critically ill* patients, insufficient autophagy [34] may cause inadequate removal of damaged proteins and mitochondria and may explain prolonged recovery or lack of recovery.

Immobility per se causes a decrease in muscle protein synthesis and is associated with so-called anabolic resistance, i.e. diminished protein synthesis as a response to infusion of amino acids [35]. Older critically ill patients display in addition "anabolic resistance" due to age per se, diminished suppression of muscle proteolysis by insulin [35] and diminished mitochondrial respiratory capacity [36]. It follows that advance age represents high risk for ICUAW.

13.5.1.2 Muscle Contractile Dysfunction

Muscle contractility can be suppressed by free radicals, abnormalities of Ca^{2+} sequestering, depletion of cellular energy by mitochondrial dysfunction or abnormalities of muscle membrane excitability.

Chronic inflammatory states can reduce muscle contractile force by increasing free radicals, which depress the myofibrillar function [37].

Uncoupling of excitation–contraction has a negative impact on contraction and might be an accompanying mechanism of CIM for the subpopulation of ICU patients with co-morbidities, such as COPD and CHF in whom the pre-existent abnormalities of Ca^{2+} sequestration exist [2], and these might worsen by stress-induced elevated sympathetic nerve activity in ICU [2].

13.5.1.3 Mitochondrial Dysfunction/Abnormalities

The loss of normal mitochondrial function results in depletion of cellular energy and increased production of free radicals [2]. Complexes I and IV of the respiratory chain in particular are depleted in CIM [38]. Activation of mitochondrial biogenesis seems to be important for short and late outcomes: if compensatory mechanisms of increased mitochondrial biogenesis are activated early, this has a positive effect on survival in critical illness [38]; in critically ill patients with a prolonged clinical course, markers of mitochondrial biogenesis are not upregulated [39].

13.5.1.4 Muscle Membrane Inexcitability

Direct muscle stimulation in humans detects reduced CMAP, compatible with the inexcitability of sarcolemma [40, 41]. Reduction of voltage-gated sodium channels was demonstrated in patients with sepsis in vitro [42]. Sodium channelopathy hypothesis also has support within experimental rat models (sepsis, steroid-denervation experiments) in which inactivation of sodium channels and, consequently, sarcolemma inexcitability were detected [5].

13.5.2 CIP

CIP is a distal axonal sensorimotor polyneuropathy affecting the limb and respiratory muscles. Abnormalities in action potential may occur within hours in humans [17]. Reversible inactivation of sodium channels was demonstrated on an experimental model of CIP in rat [43]. In some patients, weakness subsides when the global health is restored, but a subgroup of patients do not regain normal function even after 1–2 years [2]. As already stated, the current view is that CIP is not an isolated event but an integral part of multiorgan dysfunction syndrome, and the precise mechanisms are not known. Diabetes mellitus as a pre-existing morbidity predisposes to CIP, and the severity of CIP corresponds to serum glucose levels [6].

13.5.2.1 Microvascular Injury and Membrane Depolarisation Defect

Microvascular injury of the nerve, mediated by endotoxins, inflammatory mediators (tumour necrosis factor-α, serotonin and histamine), toxins and drugs, hyperglycaemia and ROS, causes hypoperfusion and lack of oxygen. Accumulation of potassium and acidic metabolites in the endoneurium leads to depolarisation of the nerve membrane and nerve dysfunction [2]. The hypothesis of (micro)vascular injury is supported by increased expression of E-selectin in the endothelial cells of endoneurial microvessels and epineurial small-calibre vessels of critically ill patients [44]. E-selectin mediates the initial step of leucocyte adhesion and extravasation to the endoneurial space, which leads to endoneurial cytokine production and tissue injury during sepsis [44].

13.6 Biomarkers

At present, no validated biomarkers for CIM/CIP are available [6]: creatine kinase may be raised in CIM and slightly also in CIP, but is not a good biomarker; biomarkers of axonal injury, plasma levels of neurofilaments, are elevated in patients with ICUAW, but early diagnosis of ICUAW, before muscle strength assessment, is not possible using neurofilament levels in plasma, and the marker also does not differentiate between CIP and CIM; a possible future candidate may be stress-induced cytokine, growth and differentiation factor-15 (GDF-15) [45].

13.7 Prevention and Therapy

- Aggressive treatment of sepsis is considered to be a cornerstone in prevention of ICUAW [6].
- Insulin treatment for normalising glycaemia is complex and difficult to perform optimally. It seems that absolute normoglycaemia is not the optimal choice, since patients treated to strict normoglycaemia had a worse outcome than patients treated to slightly higher blood glucose levels [46]. Continuous monitoring of blood glucose versus intermittent is under discussion and additional research is needed, if continuous monitoring of blood glucose is to become a routine part of daily practice in the management of critically ill patients [6].
- Reducing the duration of immobilisation can be achieved by decreasing the levels of sedation, and overall beneficial effects have been demonstrated [47].
- Early passive and active exercise trainings (such as bedside ergometer) improve muscle strength at hospital discharge [48].
- Electrical muscle stimulation may be used to activate muscles during the period when patients are not able to cooperate, but the evidence remains inconclusive and more research is necessary [6, 49].
- Late parenteral nutrition accelerates recovery compared to early parenteral nutrition [50] since it reduces muscle weakness (but not atrophy) and accelerated

recovery may be mediated by more efficient activation of autophagic quality control of myofibres.

Highlights

- Clinicians should be aware that intensive care muscle weakness can be due to different causes.
- A myopathy or a polyneuropathy can be the underlying mechanism of this flaccid weakness.
- Although the myopathy is acute, the time of onset is difficult to determine.
- Critical illness myopathy can be part of loss of myosin thick filaments or due to generalised reduction of sarcolemma excitability.

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Part III

Neurogenic Disorders

14 Idiopathic Chronic Immune-Mediated Neuropathies: Chronic Inflammatory Demyelinating Polyradiculoneuropathy and Multifocal Motor Neuropathy

Eduardo Nobile-Orazio and Francesca Gallia

14.1 Chronic Inflammatory Demyelinating Polyradiculoneuropathy

14.1.1 Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic demyelinating neuropathy which is deemed to be caused by an immune attack against peripheral nerve myelin [1–3]. It is a rare neuropathy with a prevalence ranging from 0.8/10,000 in Japan [4] to 8.9/100,000 in Olmstead County, USA [5]. CIDP usually presents with a relatively symmetric chronic relapsing or chronic progressive sensorimotor impairment that evolves over the years and that, if untreated, may lead to a consistent disability. A few different clinical presentations have been reported [3, 6] broadening the spectrum of CIDP. These include multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy also known as Lewis-Sumner syndrome, distal acquired demyelinating symmetric (DADS) neuropathy, pure motor CIDP, pure sensory CIDP including chronic immune sensory polyradiculopathy (CISP) and focal CIDP. These forms are currently considered to be variants of CIDP, even if the presence of some differences in their response to therapy does not permit to exclude that they represent different forms of demyelinating neuropathies.

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14.1.2 Clinical Presentation

CIDP may have a chronic progressive or relapsing course [1]. Initial symptoms may progress over several weeks to months even if the rapid progression over a few days or weeks may initially lead in some patients to the diagnosis of GBS [7]. The subsequent relapsing course eventually leads to the diagnosis of CIDP. This may occur in up to 16 % of all CIDP patients and should be suspected if deterioration continues >2 months from onset or if ≥3 treatment-related fluctuations occur [7]. Prominent sensory symptoms and signs at presentation should also raise this suspicion.

Typical CIDP presents with symmetric sensory and motor symptoms. Cranial nerve symptoms occur in a minority of patients, even if, when present, they may raise the suspicion of CIDP. Gait unbalance and upper limb tremor may occur in some patients while pain is relatively infrequent. Respiratory failure and symptoms of dysautonomia seldom occur in CIDP. In over 80 % of the patients, fatigue is a relevant symptom.

On examination, both proximal and distal weaknesses are common, usually in a symmetric manner. The presence of proximal weakness is one of the clues to the diagnosis of CIDP in patients with chronic neuropathy. Distal weakness is however more common and severe than proximal weakness. Reflexes are historically deemed to be absent in CIDP even if total areflexia only occurs in 70 % of patients. Sensory deficits are present in over 80 % of patients, with vibratory impairment more common than deficits to pinprick. A postural action tremor in the upper limb is present in some patients. Occasional patients may have clinical or MRI evidence of central nervous system (CNS) demyelination.

CIDP is a severe disease with over 50 % of the patients having at least temporary severe disability in the course of the disease including temporary restriction to a wheelchair or inability to walk without support, and approximately 10 % become persistently disabled or die because of the illness [8, 9]. A few patients have however a disturbing but functionally indolent course with minimal weakness and minor sensory symptoms.

14.1.3 Variants of CIDP

14.1.3.1 Sensory CIDP

Some patients with CIDP may present with a pure sensory syndrome with a prevalence ranging 5–35 % [3, 6]. Most of these patients have however electrodiagnostic evidence of demyelination also on motor nerves [10]. A few patients have a clinically and electrodiagnostically pure sensory neuropathy responding to immune therapy and are considered to have a purely sensory CIDP [11]. Some of these patients eventually evolve into typical CIDP, while others remain purely sensory during the follow-up. A particular form is chronic immune sensory polyradiculopathy (CISP) characterized by sensory symptoms, normal nerve conduction studies, delayed somatosensory evoked potentials, increased cerebrospinal fluid (CSF) proteins and response to immune therapy. Lumbar magnetic resonance imaging (MRI)

may reveal an enlargement of lumbar roots, and the inflammatory nature of the process was confirmed by root biopsy [12].

14.1.3.2 Motor CIDP

Up to 10 % of the patients have a purely motor impairment throughout the course of the disease [6]. Most of these patients were reported to worsen after steroids and to improve with intravenous immunoglobulins [13] raising the possibility that this variant may represent a diffuse variant of MMN more than a motor form of CIDP.

14.1.3.3 Focal CIDP

Occasional patients have been reported with a focal distribution of weakness and sensory loss that are restricted to one or both arms. Thomas et al. [14] reported nine patients including seven who improved with steroids or IVIg.

14.1.3.4 Lewis-Sumner Syndrome

Lewis and colleagues [15] reported five patients with a chronic, acquired, asymmetric sensorimotor demyelinating polyneuropathy. Electrodiagnostic studies demonstrated multifocal conduction block in motor nerves with normal conduction velocities. Two patients improved after therapy with prednisone. This disease is currently known as Lewis-Sumner syndrome or MADSAM neuropathy and is considered a variant of CIDP. Only part of the patients eventually evolve into CIDP, while the others maintain a multifocal distribution [16].

14.1.3.5 Distal Acquired Demyelinating Symmetric (DADS) Neuropathy

This term refers to a slowly progressive predominantly distal symmetric sensory ataxic demyelinating neuropathy often associated with upper limb tremor [17]. This phenotype is frequently observed in patients with neuropathy associated with IgM monoclonal gammopathy and antibodies to the myelin-associated glycoprotein (MAG) [18]. Patients without IgM monoclonal gammopathy or anti-MAG antibodies are considered to have a variant of CIDP that tend to have a less satisfactory response to the therapy than typical CIDP.

14.1.4 CIDP with Associated Diseases

CIDP may coexist with a number of other diseases [19]. In most of these conditions, the pathogenesis of the neuropathy is considered to be the same of CIDP. These diseases include diabetes mellitus, HIV infection, chronic active hepatitis, IgG or IgA monoclonal gammopathy of undetermined significance (MGUS), systemic lupus erythematosus or other connective tissue diseases, sarcoidosis, thyroid disease, inflammatory bowel disease, membranous glomerulonephritis or organ transplantation. In these conditions treatment is the same than in idiopathic CIDP with the only caution derived from the possible effect of treatment on the associated condition. In other conditions the pathogenesis and pathology may be different from

CIDP and therapy is directed at treating the associated disease. These include infection with *Borrelia burgdorferi*, IgM monoclonal gammopathy with anti-MAG antibodies, POEMS syndrome, osteosclerotic myeloma and other haematological and non-haematological malignancies.

14.1.5 Aetiology and Pathogenesis

There is a general consensus that CIDP is an immune-mediated disorder affecting the peripheral nerve myelin [2, 3, 6] as mainly confirmed by the fact that the vast majority of patients improves with immune therapies. Pathological studies on nerve biopsy of affected patients revealed the presence of infiltrates of macrophages and T-cell infiltrates and of deposits of Ig, and experimental studies on animals have demonstrated a similarity of CIDP with chronic experimental allergic neuritis induced in animals by immunization with nerve antigens [2]. Antibodies against a several myelin antigens have been reported in patients with CIDP, but none of them were consistently associated with CIDP [2, 3]. More recently attention has been devoted to antibodies directed against myelin or axonal proteins at the node of Ranvier including contactin-1 (CNTN1) [20] and neurofascin-155 (NF155) [21]. Even if these antibodies are only found in approximately 5 % of the patients [6], they are associated with some distinctive features including a severe motor weakness, poor response to IVIg and, in those with anti-NF155 antibodies, the frequent presence of tremor. These data were recently confirmed on a large series of Japanese patients with CIDP [22] supporting the hypothesis that different antibodies may underlie different forms of CIDP and that these forms may have different response to therapy.

14.1.6 Diagnosis of CIDP

Even if the diagnosis of CIDP is often easy in the clinical practice, the use of expensive therapies for this disease and the description of a number clinical variants have led to the proposal of several diagnostic criteria to include under this diagnosis and treat as many patients as possible trying at the same time not to include patients with similar but different neuropathies. This is why at least 15 diagnostic criteria for CIDP [23] have been proposed. The most frequently adopted criteria of the EFNS/PNS [24] (Tables 14.1 and 14.2) have the advantage of allowing the diagnosis of CIDP with only clinical and electrophysiological findings, to include patients with typical and atypical presentation of CIDP and with demyelinating abnormalities in a single nerve when other supportive criteria for the diagnosis of CIDP are present. Other parameters may help in the diagnosis of CIDP including elevated levels of CSF proteins in the cerebrospinal fluid (CSF) with normal leucocyte count, enhancement and/or hypertrophy of nerves, plexus or nerve roots on MRI or ultrasound, evidence of demyelination on sensory conduction studies, delayed somatosensory evoked potentials (SSEP), evidence of demyelination on nerve biopsy and response to immune therapy. These parameters are only necessary however when the diagnosis is not possible with clinical and electrophysiological findings.

Table 14.1 EFNS/PNS (2010) Clinical diagnostic criteria for CIDP

(1) Inclusion criteria
(a) Typical CIDP
Chronically progressive, stepwise or recurrent symmetric proximal and distal weaknesses and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected
Absent or reduced tendon reflexes in all extremities
(b) Atypical CIDP (still considered CIDP but with different features). One of the following, but otherwise as in (a) (tendon reflexes may be normal in unaffected limbs)
Predominantly distal (distal acquired demyelinating symmetric, DADS)
Asymmetric (multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), Lewis-Sumner syndrome)
Focal (e.g. involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb)
Pure motor
Pure sensory (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron)
(2) Exclusion criteria
Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin exposure likely to have caused the neuropathy
Hereditary demyelinating neuropathy
Prominent sphincter disturbance
Diagnosis of multifocal motor neuropathy (MMN)
IgM monoclonal gammopathy with high-titre antibodies to myelin-associated glycoprotein (MAG)
Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and nondiabetic lumbosacral radiculoplexus neuropathies. PNS lymphoma and amyloidosis may occasionally have demyelinating features

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14.1.7 Treatment of CIDP

Several controlled studies and retrospective studies on large series of patients have shown the efficacy of steroids, plasma exchange and IVIg in CIDP (reviewed in [25–27]) with approximately 50–70 % of the patients responding to each of these treatments. In addition almost 50 % of patients not responding to one of these treatments respond to the second therapy used leading to 80 % the proportion of patients improving with these therapies [28].

It is often difficult for the clinician to decide what therapy should be first used in CIDP. This decision should consider the efficacy, cost, side effects and duration of the benefits of each therapy. A few randomized trials have shown a comparable short-term efficacy of IVIg and oral corticosteroids [29] and of IVIg and plasma exchange [30] and that both IVIg and steroids have prolonged efficacy in CIDP. A randomized controlled trial comparing the 6-month efficacy of IVIg and intravenous methylprednisolone showed that IVIg was more frequently effective and tolerated than steroids during the first 6 months of treatment, although, when effective, steroids were less frequently associated with deterioration than IVIg after therapy

Table 14.2 EFNS/PNS (2010) Electrodiagnostic criteria for CIDP

(1) Definite: at least one of the following
(a) Motor distal latency prolongation ≥50 % above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome)
(b) Reduction of motor conduction velocity ≥30 % below LLN in two nerves
(c) Prolongation of F-wave latency ≥20 % above ULN in two nerves (≥50 % if amplitude of distal negative peak CMAP <80 % of LLN values)
(d) Absence of F-waves in two nerves if these nerves have distal negative peak CMAP amplitudes ≥20 % of LLN + ≥ 1 other demyelinating parameter[a] in ≥1 other nerve
(e) Partial motor conduction block: ≥ 50 % amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP ≥20 % of LLN, in two nerves, or in one nerve + ≥ 1 other demyelinating parameter[a] in ≥1 other nerve
(f) Abnormal temporal dispersion (>30 % duration increase between the proximal and distal negative peak CMAP) in ≥2 nerves
(g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥1 nerve (median ≥6.6 ms, ulnar ≥6.7 ms, peroneal ≥7.6 ms, tibial ≥8.8 ms) + ≥ 1 other demyelinating parameter[a] in ≥1 other nerve
(2) Probable
≥30 % amplitude reduction of the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak CMAP ≥20 % of LLN, in two nerves, or in one nerve + ≥ 1 other demyelinating parameter[a] in ≥1 other nerve
(3) Possible
As in (1) but in only one nerve

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CMAP compound muscle action potential, *ULN* upper limit of normal values, *LLN* lower limit of normal values
[a]Any nerve meeting any of the criteria (*a–g*)

discontinuation [31]. These data were confirmed in the follow-up extension of the study [32] showing that a similar proportion of patients eventually deteriorated after discontinuing IVIg (87 %) or IVMP (79 %) but that the median time to deterioration was longer after discontinuing IVMP (14 months) than IVIg (4.5 months). Plasma exchange is often considered the third choice since it is more invasive for the patients and has a higher prevalence of side effects that makes it less suitable for the long-term treatment of the patients [24].

The possibility to reduce the inconvenience of repeated hospital admissions for maintenance of IVIg therapy can be resolved in most patients with home injection of subcutaneous immunoglobulin (SCIg) whose efficacy was confirmed in a small randomized study [33].

Several anecdotal reports have shown the efficacy of other immune therapies that have been used to reduce the cost and frequency of IVIg and the side effects of steroids or to treat patients not responding or becoming resistant to these therapies (reviewed in [34]). The preliminary positive results were only marginally confirmed in a large retrospective studies showing that only 20–30 % of the patients treated with these therapies improved while a consistent proportion of patients had to suspend them for adverse events [35]. In addition none of the controlled study with

immune therapy in CIDP including oral azathioprine, oral methotrexate and intramuscular interferon beta-1a showed a significant benefit over placebo [34].

More recent reports have shown the efficacy in some patients of new immune therapies including fingolimod, natalizumab and autologous haematopoietic stem cell transplantation. These data should be however confirmed in controlled studies considering that up to 40 % of the patients may go into remission without therapy and that some of these therapies may cause relevant adverse events.

14.2 Multifocal Motor Neuropathy

14.2.1 Introduction

The term multifocal motor neuropathy (MMN) was first introduced in 1988 by Pestronk et al. [36] who described two patients with a progressive purely motor, predominantly distal, asymmetric neuropathy with multifocal persistent conduction blocks (CB) on motor but not sensory nerves. Even if a few similar patients had been previously reported, Pestronk et al. first highlighted the frequent association with anti-GM1 IgM antibodies and the response to immune therapies. MMN was originally related to CIDP or to motor neuron disease (MND), but it is now considered a well-defined separate clinical entity [37, 38].

14.2.2 Clinical Features

MMN is a rare neuropathy with a prevalence of 0.6 per 100,000 inhabitants [39]. MMN almost invariably presents with progressive, usually distal, asymmetric weakness in the upper limbs in the distribution of individual and often not contiguous motor nerves [37, 38]. Some patients may however present with more proximal weakness or with symptoms in their legs. The disease usually have a progressive course affecting other nerves but may also have a stepwise progression with intervals of months or even years, while occasional patients may even have a remitting course. Localized muscle atrophy may be mild or irrelevant in the early stage of the disease. Fasciculations, cramps and myokymia have been variably reported in these patients making the similarity of MMN with MND more evident. The clinical distinction may become even more difficult in the 20–30 % of patients who have brisk tendon reflexes, while in the majority of patients, reflexes are reduced in a patchy way or diffusely. Cranial nerve involvement or respiratory failure due to unilateral or bilateral phrenic nerve palsy may seldom occur. One of the typical features of this neuropathy is the absence of sensory impairment even in the territory of affected sensorimotor nerve. Some patients may report mild sensory symptoms but only a minority of them have a definite though minor sensory loss. From the list of these symptoms, it is not surprising that several patients receive a diagnosis of MND or entrapment neuropathy, before they receive the correct diagnosis [39].

Most patients with MMN carry an overall good prognosis *quoad vitam*, even if the majority of them become disabled in their daily life because of a reduced dexterity in manual activities, while very few of them become disabled in walking [37].

14.2.3 Diagnosis of MMN

The most commonly used diagnostic criteria for MMN have been proposed by the Joint Task Force of the EFNS/PNS (Tables 14.3 and 14.4) [40]. As in the case of CIDP, these criteria allow the diagnosis of MMN only with clinical and electrophysiological studies. In particular the presence of persistent, multifocal, partial conduction blocks (CB) in motor nerves outside the usual sites of nerve compression is the mainstay of this diagnosis. CB is not specific for MMN but can be also found in other demyelinating neuropathies including CIDP and Guillain-Barré syndrome (GBS), where it is associated with more diffuse signs of demyelination that in MMN, when present, are typically restricted in the nerve with CB. Sensory nerve conduction studies are usually normal or only minimally affected in MMN, even in the nerves with motor CB [37].

Other tests may help in the diagnosis of MMN when clinical and electrophysiological findings are inconclusive. Moderately increased serum creatine kinase activity is found in up to two thirds of patients, while CSF proteins are moderately increased (usually up to 80 mg/dl) in one third of the patients [37]. The most typical

Table 14.3 EFNS/PNS (2010) Clinical diagnostic criteria for MMN

Core criteria (both must be present)
1. Slowly progressive or stepwise progressive, asymmetric limb weakness or motor involvement having a motor nerve distribution in at least two nerves, for more than 1 month[a]
2. No objective sensory abnormalities except for minor vibration sensory abnormalities in the lower limbs
Supportive clinical criteria
3. Predominant upper limb involvement[b]
4. Decreased or absent tendon reflexes in the affected limb[c]
5. Absence of cranial nerve involvement[d]
6. Cramps and fasciculations in the affected limb
Exclusion criteria
7. Upper motor neuron signs
8. Marked bulbar involvement
9. Sensory impairment more marked than minor vibration loss in the lower limbs
10. Diffuse symmetric weakness during the initial weeks

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[a]Usually more than 6 months
[b]At onset, predominant lower limb involvement accounts for nearly 10 % of the cases
[c]Slightly increased tendon reflexes, in particular in the affected arm, have been reported and do not exclude the diagnosis of MMN provided criterion 7 is met
[d]12th nerve palsy reported

Table 14.4 EFNS/PNS (2010) Electrophysiological criteria for conduction block

1. Definite motor CB
Negative CMAP area reduction on proximal versus distal stimulation of at least 50 % whatever the nerve segment length (median, ulnar and peroneal). negative CMAP amplitude on stimulation of the distal part of the segment with motor CB must be >20 % of the lower limit of normal and >1 mV (baseline negative peak) and an increase of proximal negative peak CMAP duration must be ≤30 %
2. Probable motor CB
Negative CMAP area reduction of at least 30 % over a long segment of an upper limb nerve with an increase of proximal negative peak CMAP duration ≤30 % OR Negative CMAP area reduction of at least 50 % (same as definite) with an increase of proximal negative peak CMAP duration >30 %
3. Normal sensory nerve conduction in upper limb segments with CB and normal SNAP amplitudes (see exclusion criteria)

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Evidence for conduction block must be found at sites distinct from common entrapment or compression syndromes

laboratory finding is the presence of increased levels of serum IgM antibodies to the ganglioside GM1 with frequency in most laboratory of 40–50 % [37, 38]. These antibodies are not specific for MMN as they can be found in 5–10 % of patients with MND. More recently the combination of GM1 with galactocerebroside has been reported to increase the sensitivity of anti-GM1 testing to approximately 75 % of MMN patients with only a marginal reduction of their specificity [41]. Testing for anti-GM1 antibodies may help in the diagnosis in patients in whom the clinical and electrophysiological data are not conclusive, even if their absence does not exclude the diagnosis of MMN.

MRI and ultrasound studies of the nerves may help in revealing nerve abnormalities, particularly in the proximal segment of the nerves not easily accessible to nerve conduction studies [40]. Nerve biopsy is seldom useful as it is routinely performed on the sural or other sensory nerves, which are typically normal in MMN. Biopsy of motor nerves may help in the distinction of MMN from MND showing a significantly higher density of clusters of regenerative small myelinated fibres in MMN than in MND [42].

14.2.4 Aetiology and Pathogenesis

The frequent association of MMN with anti-GM1 antibodies and the frequent improvement after IVIg support the opinion that the disease is immunologically mediated and possibly caused by anti-GM1 IgM binding to neural structures [37, 38]. It remains however unclear what may cause the disease in patients without these antibodies and what may impair motor nerve conductions in experimental studies in the sera of patients with MMN not only with but also without high anti-GM1 antibodies [43]. It is therefore likely that the sera from patients with MMN

contain soluble factors able to affect the neural transmission even if the role of anti-GM1 antibody in this blocking effect remains unclear.

14.2.5 Therapy

Almost 80 % of patients with MMN respond to IVIg, whose efficacy has been confirmed in five randomized controlled studies [44]. IVIg induces a rapid improvement which often occurs within 1 week of treatment and is usually more evident in recently affected regions. Only a few patients have persistent improvement after a single or few courses of therapy, while in most patients, their effect has to be maintained with periodic IVIg infusions for long periods of time, if not indefinitely [45, 46]. Maintenance therapy can be also performed at home with SCIg whose efficacy has been confirmed in two controlled studies [47, 48]. Several patients become however progressively less responsive to IVIg and require increasing dosage or frequency of IVIg to maintain improvement.

There are not real alternatives to the use of IVIg in MMN [49]. Steroids are ineffective and potentially harmful in MMN with almost 20 % of the patients worsening after this therapy. Similarly ineffective and sometime harmful is plasma exchange. This highlights the importance of a correct distinction of MMN from CIDP and Lewis-Sumner syndrome where steroids and plasma exchange are effective. Cyclophosphamide was initially reported to be effective in MMN [36] but has several side effects that make it unsuitable for nonfatal disorders such as MMN [40]. A few anecdotal or open-label studies report the efficacy in some patients of azathioprine, interferon-β1a (IFN-β1a), methotrexate, rituximab and eculizumab (reviewed in [49]). The only randomized controlled trial with immune suppressants in MMN showed however that mycophenolate mofetil did not permit to increase the effectiveness or to reduce the dose of IVIg [50]. A recent Cochrane review concluded that there is so far little evidence that any immunosuppressant may be useful in MMN [49], confirming that immunoglobulin therapy remains the gold standard for the treatment of MMN.

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Immune Neuropathies

15

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15.1 Introduction

Immune neuropathies, also known as acquired neuropathies, are so called based on the fact that antibody-/immune-mediated mechanisms underlie the pathogenesis of the neuropathy. In general, these patients usually present with sensory and motor symptoms, in a distal-to-proximal ("ascending") fashion, although variants have been described. Immune neuropathies differ from inherited neuropathies in several ways – clinically, electrodiagnostically, and by pattern of progression and treatment response. Immune neuropathies, as opposed to inherited neuropathies, present acutely (with a prior period of "normalcy"), faster progression (accelerated worsening in a span of 4–8 weeks), and with either spontaneous remission or response to treatment with immunomodulators. Electrodiagnostically, nonuniform slowing, presence of conduction blocks, temporal dispersion, and impersistent or absent F-wave responses are usually noted. Several forms of immune neuropathies are noted: (1) Guillain-Barre syndrome (acute immune-mediated demyelinating polyneuropathy (AIDP) or acute inflammatory demyelinating polyneuropathy) and its variants, (2) chronic inflammatory demyelinating polyneuropathy (CIDP) and its variants, and (3) other dysimmune neuropathies, secondary to specific antibodies. Although a majority of the cases are seen in the adult patients, occasional pediatric cases are encountered as well. The specific clinical presentation and etiology in the pediatric population may be different than in the adult patients, but they are not discussed here in detail and are beyond the scope of this chapter.

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15.1.1 Guillain-Barre Syndrome (GBS, Also Known as AIDP)

15.1.1.1 Epidemiology

The incidence of Guillain-Barre syndrome (GBS) varies between 0.6 and 4/100,000 according to different studies [1]. Males are slightly more affected than females. The age of onset of symptoms is bimodal with peak incidence between 15–24 years and 65–74 years [2]. Previous respiratory illnesses, mainly flu-like symptoms and gastroenteritis (due to *Campylobacter jejuni* infections), are reported in the period prior to onset of symptoms [3]. Other viruses or bacteria-related infection, confirmed in studies, preceding GBS include *Cytomegalovirus*, *Epstein-Barr virus*, *Varicella zoster virus*, and *Mycoplasma pneumoniae*. Vaccination as an inciting factor underlying GBS presentation has been discussed. There was a concern about the increase in GBS cases after the swine flu vaccine given in 1976 in the USA, but a study published in 1998 showed that the risk of GBS associated with influenza vaccination was very small and was attributed to 1.1 case per 1 million persons vaccinated against influenza [4]. However, this information must be borne in mind in light of the fact that a nervous tissue-derived rabies vaccine (rabies virus-infected suckling mouse brain (SMB) and phenol-inactivated rabies virus-infected mature goat or sheep brain) is still an important cause of GBS, and it is reported to be 1 in 1000 cases.

15.1.1.2 Clinical Presentation of GBS

Classical GBS or AIDP

Acute immune-mediated demyelinating polyneuropathy (AIDP) is the most common form of GBS in Europe and North America. AIDP is a monophasic illness, characterized by rapidly progressive bilateral and symmetric weakness of the limbs, with loss of reflexes (if reflexes are preserved during the course of the disease, one should think about another diagnosis). Among the cranial nerves, mainly the facial nerve can be involved, although other cranial nerves are affected, rarely. Respiratory muscles are affected in about 25 % of the cases. About a third of the patients would require intubation. In patients with impending respiratory failure, frequent monitoring of forced vital capacity and negative inspiratory force is required to predict the need for intubation. The weakness reaches a plateau between 2 and 4 weeks from symptom onset [5].

Pain is increasingly found to be a common symptom in GBS and other forms of GBS such as Miller-Fisher syndrome (MFS), but it is usually under-recognized because of the present concomitant weakness. It can be present in the prodromal stage before onset of weakness, and it can last for months after the resolution of the weakness. It is more prevalent in more severe cases and when sensory symptoms are present. Pain can take different forms including painful paresthesia, radicular pain, muscle pain, and arthralgia.

Autonomic dysfunction affects about two-thirds of patients with GBS, and it is not always readily recognized. If unrecognized, autonomic dysfunction in GBS patients can lead to life-threatening situations. The autonomic cardiovascular

complications that can occur in GBS include bradyarrhythmias, tachyarrhythmias, hypertension, and orthostatic hypotension, with sensitivity to vasoactive agents. Patients with severe paralysis are more prone to have autonomic dysfunction, and for this reason, patients with weakness should be monitored under telemetry until improvement. Other autonomic dysfunction symptoms include urinary retention and ileus [6].

The diagnosis of AIDP is mainly clinical as additional testing such as lumbar puncture and nerve conduction studies might not help with diagnosis in the first few days of the illness. Elevated protein in the CSF (>100 mg/dl) remains the hallmark for diagnosis. The typical cyto-albuminologic dissociation reported in GBS is seen in less than 50 % of cases in the first day of the disease and in 80 % of cases by 2 weeks [7]. However, lumbar puncture helps in eliminating pleocytosis which could indicate another diagnosis such as infection as well. A white cell count above 50 cells/microl is less likely to be related to AIDP.

On nerve conduction studies, the typical demyelinating features (i.e., prolonged distal latency, evidence of conduction block on proximal stimulation, temporal dispersion of compound muscle action potential, and demyelinating range velocity) are noted. However, some of these features may not be present in the first 10 days of symptom onset. The early signs on NCS observed in the first 7 days of the disease include absence of H-reflex (in 97 % of the cases), prolonged F-wave latency, absence of F-wave response (in 84 % of the cases), presence of an A-wave, and abnormal sensory response in the upper extremity with fairly preserved sural sensory response. Of the demyelinating features, prolongation of distal latencies and temporal dispersion of the distal CMAP are the earliest demyelinating features seen in early AIDP. Blink reflex studies are often helpful. On blink reflex study, absent or prolonged ipsilateral R1 and R2 responses and contralateral R2 responses are noted in about half of the patients. Blink reflex response might be abnormal even with normal facial nerve function clinically. On needle electromyography (EMG), fibrillations and positive sharp waves can be noted if low or absent CMAP is observed; otherwise, it might take 2–4 weeks for a spontaneous activity to be evident on EMG [8].

15.1.2 GBS Variants

15.1.2.1 Acute Motor Axonal Neuropathy (AMAN)

AMAN constitutes the most common variant of GBS along with AIDP. It has been described in northern China rural areas where 36 patients were affected in a summer epidemic. This form is more prevalent in East Asia and Central and South America [9]. This form of GBS is characterized by more rapid onset, with a nadir reached earlier. Cranial nerves are less frequently involved, and weakness tends to be more distal than proximal. There is no sensory involvement clinically although some patients report “pins and needles” sensation distally in limbs. On electrodiagnostic studies, loss of amplitudes and diffuse fibrillation potentials and positive sharp waves are noted in limb muscles.

Recovery can take two paths: rapid recovery or poor and slow recovery. The rapid recovery could be secondary to the resolution of conduction block at the nodes of Ranvier after treatment [10]. *Campylobacter jejuni* infection is most frequently seen in this variant with gastrointestinal symptoms reported in 85 % of cases in the 4 weeks preceding the weakness. Anti-GM1 antibody is seen in 60 % of the cases, reinforcing the molecular mimicry of human gangliosides on the peripheral nerves by *Campylobacter jejuni* lipo-oligosaccharide [11]. This variant of GBS responds best to IVIG, more than plasmapheresis.

15.1.2.2 Acute Motor Sensory Axonal Neuropathy (AMSAN)

AMSAN is similar to AMAN, but it is characterized by sensory involvement, in addition to the motor component. IVIG remains the mainstay of treatment.

15.1.2.3 Miller-Fisher Syndrome (MFS) and Bickerstaff's Brainstem Encephalitis (BBE)

Miller-Fisher syndrome (MFS), described by Fisher in 1956 [12], is a variant of GBS characterized by the clinical triad of ataxia, areflexia, and ophthalmoplegia. MFS constitutes 5–10 % of GBS cases in Western countries, but higher incidence is reported in Eastern Asia (25 % in Japan) [13]. A prior infection 10–14 days prior to the onset of the symptoms is common. Recent *Campylobacter jejuni* or *Haemophilus influenzae* infections have been reported in 18 % of the cases [14] and in 7 % of the cases of MFS, respectively [15].

The clinical symptoms include diplopia, ataxia, and ptosis. Other symptoms include facial palsy, dysesthesia in the limbs, dysphagia, photophobia, and decrease in superficial and deep sensation, weakness, and autonomic dysfunction. The presence of muscle weakness in MFS indicates the overlap between MFS and GBS. The course of MFS is benign: In a case series following patients with MFS, ataxia and ophthalmoplegia are resolved by 6 months of follow-up [16]. In typical MFS, the strength is normal, and motor nerve conduction study is usually normal, although the intensity of the stimulus required to generate a maximal compound muscle action potential might be higher compared to normal [17].

Anti-glycolipid antibody "anti-GQ1b IgG antibody" has been associated with MFS [18, 19]. Anti-GQ1b IgG antibody tends to peak at clinical presentation as early as 2 days from symptom onset and disappears by 1 month from symptom onset. Serum of patients with MFS is positive for anti-GT1a IgG antibody. It has been shown in studies that anti-GQ1b and anti-GT1a IgG antibodies cross-react with other antigens. GQ1b antigen is mostly concentrated on the oculomotor, trochlear, and abducens nerves which explain the ophthalmoplegia seen in MFS and GBS associated with ocular involvement. Treatment of MFS is extrapolated from treatment of GBS as no randomized trials are available [13]. Mild cases can be treated with conservative approaches. More severe cases (severe ataxia, profound bulbar palsy) can be treated with plasmapheresis or intravenous immunoglobulin.

Bickerstaff's brainstem encephalitis (BBE) shares with MFS the "ophthalmoplegia," the "ataxia," and the presence of anti-GQ1b IgG antibody in the serum. To establish the diagnosis, disturbance of consciousness or hyperreflexia is required.

BBE was described initially in 1951 and afterward in 1957 by Bickerstaff, and the reported cases almost all had ataxia, ophthalmoplegia, and alteration of consciousness. In the largest case series of BBE reported by [20], the clinical features of BBE are as follows: Preceding upper respiratory infection was the most common prodromal infection. Recent history of *Campylobacter jejuni* infection was found in 23 % of cases. In one-third of the cases, patients were in stupor, semicoma, or coma. In one-third of the cases, reflexes were brisk (the rest had normal, hyporeflexia, or absent reflexes). Babinski sign was present in 40 % of the cases. Limb weakness was present in 60 % of cases. Other signs included ptosis, bulbar palsy, facial palsy, and deep and superficial sensory impairments. All cases had ataxia and ophthalmoplegia. In the presence of associated limb weakness, electrodiagnostic studies showed mainly an axonal process. Brain MRI shows hyperintense lesions on T2-weighted images in the brainstem, thalamus, cerebellum, and white matter of the cerebrum. Perivascular lymphocytic infiltration with perivascular edema and glial nodules has been reported on autopsy in the brainstem. Treatment involves steroids, plasmapheresis, IVIG, or combination of these therapies. Complete remission is seen in about 60 % of patients after 6 months from onset of symptoms.

15.1.2.4 Pharyngeal-Cervical-Brachial Variant

This specific form is considered by some authors as a variant of GBS with some features of Miller-Fisher syndrome [21–25]. Usually, infection precedes the onset of weakness (respiratory infection > diarrheal illness), and *Campylobacter* infections are more common than viral infections. As the name implies, the bulbar, neck, and arm muscles are affected, resulting in dysphagia and proximal-predominant upper extremity weakness. External ophthalmoplegia and facial weakness may be observed in about 50 % of the patients. Although the legs may be relatively preserved, hip flexors are involved. Usually, no sensory loss is appreciated. Asymmetric reflexes (hyporeflexia in upper extremities and normoreflexia in the lower extremities) are noted. In addition, ataxia and autonomic dysfunction are noted in minority of the cases. CSF protein may be elevated, and nerve conduction studies may show slow conduction velocities and prolonged F-wave latencies. IgG binding to GT1a or GM1b gangliosides are usually seen [21–23, 26]. In some ways, this entity can be considered as an "incomplete form" of the classical GBS (Table 15.1).

Table 15.1 Summary of antibodies associated with GBS variants

AIDP/GBS	Anti-GM1, other unknown antibodies
AMAN	Anti-GM1a, Anti-GM1b, anti-GD1a, anti-GalNacGD1a IgG
AMSAN	Anti-GM1a, Anti-GD1a IgG
MFS	Anti-GQ1b, anti-GT1a IgG
BBE	Anti-GQ1b IgG
BBE with limb weakness	Anti-GQ1 b, anti-GM1, anti-GD1a, anti-GalNac-GD1a IgG
Pharyngeal-cervical-brachial variant	Anti-GT1a, Anti-GM1b

15.1.3 Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

15.1.3.1 Clinical Presentation of CIDP

Chronic inflammatory demyelinating polyneuropathy (CIDP) remains a heterogeneous disease entity, with multiple variants as well. In older literature, CIDP has been reported as a "steroid-responsive neuropathy" as well, based on its response to immunomodulatory treatment. Clinical estimates suggest that CIDP affects 1–7.7 per 100,000 population [27–29]. The typical description of CIDP is a chronic, monophasic/progressive, or relapsing-remitting disease (33–65 % of cases [29, 30]), with the presence of weakness in proximal and distal muscles of limbs, in addition to sensory symptoms for more than 2 months. Men are more affected than women. Age of onset ranges from 2 to 72 years; however, a greater prevalence is noted in the fifth decade. Hyporeflexia is usually the most common finding, and about 86 % of patients have objective sensory loss on exam involving one or more sensory modalities as reported [31]. As opposed to GBS, a diarrheal/viral illness preceding the onset of weakness is not encountered. Albuminocytologic dissociation in the cerebrospinal fluid during the disease course and relapse is often noted. Electrodiagnostic studies show demyelinating features (i.e., slowing of conduction velocity to less than 70 % of normal in two or more nerves, presence of temporal dispersion, or conduction block). In a population study, ~30 % of patients show these characteristic electrodiagnostic features [31]. Taken together with clinical examination and course, only about 50 % of patients with CIDP present with this "typical" presentation [32]. The rest of the patients may have clinical and electrodiagnostic features commonly termed the "CIDP variants."

15.1.4 Major CIDP Variants

15.1.4.1 Distal Acquired Demyelinating Symmetric (DADS) Polyneuropathy

Distal acquired demyelinating symmetric (DADS) polyneuropathy is a "distal" form of CIDP. It accounts for about 2–17 % of CIDP cases. DADS is more commonly seen in older men (age greater than 65), and the onset is usually insidious and subacute/chronic. Clinically, it is characterized mainly by predominant sensory symptoms although abnormal motor nerve conduction studies (demonstrating demyelinating changes) are observed. In addition, elevated CSF protein is observed in 86 % of cases [33]. In about two-thirds of patients with DADS, an abnormal monoclonal protein (M protein) is found on serum protein electrophoresis and immunofixation. In 2/3 of those patients, antibody against myelin-associated glycoprotein (MAG) in the IgM M protein subgroup is found. DADS patients with monoclonal protein are usually men and older in age with slowly progressive disease and do not respond well to immunomodulatory therapies [34].

15.1.4.2 Lewis-Summer Syndrome or Multifocal Acquired Demyelinating Sensory and Motor (MADSAM) Neuropathy

MADSAM is another "distal" form of CIDP with onset in the upper extremities. It accounts for 6–15 % of CIDP cases. Males are commonly involved in the fifth decade. Symptoms at onset could be sensorimotor (65 % of the cases) or pure sensory (numbness, paresthesia, or neuropathic pain in 35 % of cases). Distal arms are initially affected in ~70 % of the cases. Lower extremities are affected in about 38 % of the cases [35]. The median and ulnar nerves are the most commonly involved nerves on nerve conduction studies which may lead to a diagnosis of entrapment neuropathies instead of upper limb-onset MADSAM. Cranial nerve involvement has also been reported, including the optic, oculomotor, trochlear, and trigeminal nerves. The main feature on electrodiagnostic studies is a proximal conduction block, which can be missed if proximal stimulation as proximal as Erb's point is not performed. Slow conduction velocities in the demyelinating range along with prolonged or absent F-waves are observed in the nerves with conduction block. CSF protein is normal to mildly elevated in ~33–42 % of cases. Intravenous immunoglobulin is more effective as a treatment than steroids.

15.1.4.3 Sensory-Predominant CIDP

Sensory predominant CIDP accounts for 6–12 % of CIDP cases, although the presence of this entity as a special group (also referred to as chronic immune-mediated sensory polyneuropathy (CISP)) is controversial among many. Symptoms are almost all sensory and could include the following: numbness and tingling in "stocking-glove distribution," neuropathic pain, or proprioception deficit leading to sensory ataxia. However, the muscle strength is usually normal [36]. A small case series showed that some patients in this subgroup progress to have weakness, when followed over several years [37]. On electrodiagnostic studies, demyelinating changes are seen in motor nerves as well as in sensory nerves. CSF protein may be elevated. Treatment is similar to typical CIDP, if clinically disabling. However, objective outcome measures are not usually available to evaluate progress, and thus the entity and the treatment response remain controversial.

15.1.4.4 Motor-Predominant CIDP

Similar to the CISP group, motor-predominant forms of CIDP have been described in selected cases. Motor involvement in multiple nerves, with sparing of sensory nerves, is noted. Whether this is a separate group or an intermediate form in the progression to classical CIDP or MADSAM is unclear.

15.1.4.5 Focal CIDP

Focal CIDP is described as CIDP-like features in only one limb. Both motor and sensory components are affected, both by clinical and electrodiagnostic features. Whether this variant evolves into multifocal CIDP (Lewis-Sumner syndrome) is unclear.

CIDP Diagnosis

Electrodiagnostic Criteria

In 1991, American Academy of Neurology proposed criteria for diagnosis of CIDP [38]. The electrodiagnostic criteria were linked to the clinical, pathologic, and cerebrospinal fluid studies for definite diagnosis of CIDP and included the following as mandatory criteria for a definite diagnosis:

- Must have three out of four:
  - Reduction in conduction velocity in two or more motor nerves (less than 80 % of the lower limits of normal if amplitude is more than 80 % of normal or less than 70 % of the lower limits of normal if amplitude is less than 80 % of normal)
  - Presence of partial conduction block or abnormal temporal dispersion in at least one motor nerve
  - Prolonged distal latencies in two motor nerves or more (more than 125 % of upper limits of normal if amplitude is more than 80 % of lower limits of normal or more than 150 % of upper limits of normal if amplitude is less than 80 % of lower limits of normal)
  - Absence of F-waves or prolonged F-wave latencies in two motor nerves or more (more than 120 % of upper limits of normal if amplitude is more than 80 % of lower limits of normal or more than 150 % of upper limits of normal if amplitude is less than 80 % of lower limits of normal)

However, the above-suggested criteria for diagnosis of CIDP have limitations as the sensory variant of CIDP is not included, and their sensitivity is reduced at the earlier stages of the disease. In 2010, the European Federation of Neurological Societies and Peripheral Nerve Society (EFNS-PNS) redefined the criteria for diagnosis of CIDP [39] which to date remain the most accepted diagnostic criteria for CIDP.

The EFNS criteria are as follows:

1. *Definite: at least one of the following:*
   (a) Motor distal latency prolongation ≥50 % above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome)
   (b) Reduction of motor conduction velocity ≥30 % below LLN in two nerves
   (c) Prolongation of F-wave latency ≥30 % above ULN in two nerves (≥50 % if amplitude of distal negative peak CMAP <80 % of LLN values)
   (d) Absence of F-waves in two nerves if these nerves have distal negative peak CMAP amplitudes ≥20 % of LLN + ≥1 other demyelinating parameter in ≥1 other nerve
   (e) Partial motor conduction block: ≥50 % amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP ≥ 20 % of LLN, in two nerves or in one nerve + ≥1 other demyelinating parameter in ≥1 other nerve

(f) Abnormal temporal dispersion (>30 % duration increase between the proximal and distal negative peak CMAP) in ≥2 nerves
(g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥1 nerve (median ≥6.6 ms, ulnar ≥6.7 ms, peroneal ≥7.6 ms, tibial ≥8.8 ms) + ≥1 other demyelinating parameter in ≥1 other nerve

2. *Probable*
≥30 % amplitude reduction of the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak CMAP ≥20 % of LLN, in two nerves or in one nerve + ≥1 other demyelinating parameter in ≥1 other nerve
3. *Possible*
As in (1) but in only one nerve

To apply these criteria, the median, ulnar (stimulated below the elbow), peroneal (stimulated below the fibular head), and tibial nerves on one side are tested. If criteria are not fulfilled, the same nerves are tested at the other side, and/or the ulnar and median nerves are stimulated bilaterally at the axilla and at Erb's point. Motor conduction block is not considered in the ulnar nerve across the elbow, and at least 50 % amplitude reduction between Erb's point and the wrist is required for probable conduction block.

Legend: CMAP (compound muscle action potential), ULN (upper limit of normal values), LLN (lower limit of normal values).

Other Tests to Help in Establishing the Diagnosis

Cerebrospinal fluid (CSF) studies show cyto-albumino dissociation with normal white blood cells count and high protein level in CSF in about 86–95 % in different case series [31, 33, 40]. Somatosensory-evoked potentials can be used to evaluate the presence of proximal demyelination. This is useful in cases of sensory CIDP with normal conduction studies and normal F-wave responses [41]. Magnetic resonance imaging (MRI) of the brachial or lumbar plexus may show the following findings: swelling of the brachial and/or lumbar plexus on short tau inversion recovery (STIR) and high intensity of the brachial and/or lumbar plexus on STIR or T1-weighted images without contrast enhancement or diffusion-weighted images. These findings are seen in about ~55–67 % of cases, in a case series. Other findings include mild contrast enhancement (in about 30 % of cases) after gadolinium administration. However, there is no correlation between the MRI findings and the response to treatment [42]. Nerve ultrasound shows hypertrophy of roots and/or nerves, with enlargement of the cross-sectional area [43]. In a case report, it was shown that the hypertrophy is segmental and corresponds to conduction block seen on electrodiagnostic studies [44]. The hypertrophy does not correlate (as in MRI) to the disease activity, and it persists after treatment.

Nerve biopsy shows the following: segmental demyelination, active macrophage-mediated demyelination, onion bulb proliferation of Schwann cells around demyelinated fibers (indicating demyelination and remyelination), and axonal loss.

However, the presence of "onion bulbs" is not very specific to this condition and can also be seen in inherited neuropathies and in neuropathies associated with monoclonal gammopathy. Concurrent muscle biopsy performed at the time of the nerve biopsy is usually helpful in evaluating the chronicity of the neuropathy and the amount of reinnervation (based on regenerating fibers and type grouping). Mononuclear cellular infiltrate consisting of CD4 and CD8 T lymphocytes, macrophages, and B cells is seen mainly in the perivascular space in the endoneurium, to lesser extent in the epineurium and rarely perineurium [45, 46]. The perivascular inflammatory infiltrates are nonspecific for CIDP and could be seen in acute inflammatory demyelinating polyneuropathy, monoclonal gammopathy, and vasculitis, although in the latter, larger epineurial vessels are mainly affected as reported by Krendel et al. [46]. Teased fiber preparations of biopsied nerves show segmental demyelination. In a case series reported by [31], demyelinating lesions on sural nerve biopsy were found in 48.2 % of cases and axonal lesions in 21.4 %. In addition, inflammation was observed in only 10.7 % of cases and reported to be mostly seen in proximal nerve trunk or spinal roots [47]. These findings emphasize that the histopathological diagnosis of CIDP can be challenging and should be made based on clinical presentation, in conjunction with electrodiagnostic features of demyelinating neuropathy (Figs. 15.1, and 15.2).

CIDP Pathophysiology

Based on evaluation of nerve biopsies and autopsy studies, it is known that the nerve roots and the peripheral nerves are affected. Inflammation is seen at the endoneurial, epineurial, and perivascular locations. Predominantly, T cells are present at the sites of inflammation. Segmental demyelination, thin myelin sheaths, and regenerating clusters of nerves are commonly seen in nerve biopsies. Upregulation of MHC class II expression has also been noted. Based on this pathophysiology, whether chronic immunomodulatory treatments targeting T cells selectively may be efficacious is currently under investigation (vide infra). Clinical trials involving the use of

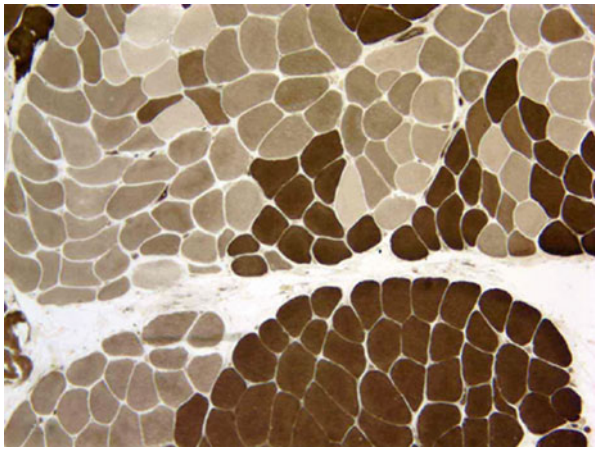
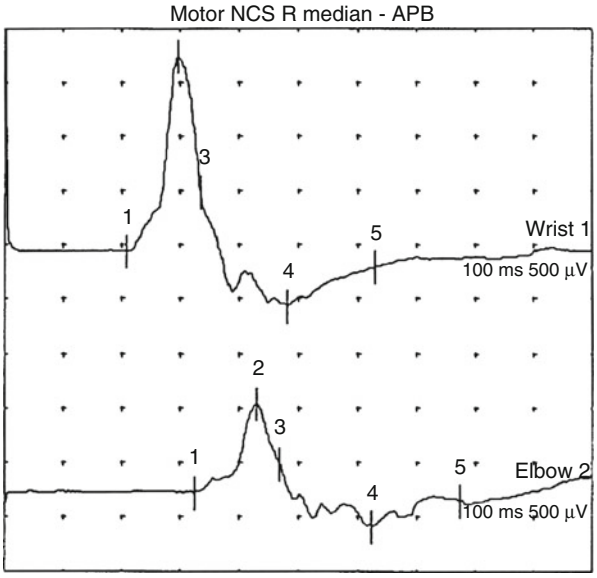


Fig. 15.1 Muscle biopsy showing type grouping in chronic denervation, followed by reinnervation. Staining of muscle section for ATPase at pH 4.6, which shows type 1 fibers in dark and type 2a fibers in light and type 2b fibers in intermediate color. The biopsy shows grouping of type 1 fibers and type 2 fibers in separate areas



Nerve/site	Recording site	Latency (ms)	Amplitude (mV)	Distance (cm)	Velocity (m/s)
Right median - APB					
Wrist (top)	APB	**21.00** (4.2)	**1.8** (5.0)	7	
Elbow (bottom)	APB	32.35	0.8	18.5	**16.3** (50)

Fig. 15.2 Temporal dispersion and conduction block in CIDP/GBS. Shown is a sample trace of median motor nerve conduction study in a patient with CIDP. Note the prolonged distal latencies, loss of amplitude, temporal dispersion (120 %), conduction block (56 % reduction), and slow conduction velocity (68 % reduced to that of lower limit of normal). The normal values for the nerve conduction study are noted within parentheses in the table

alemtuzumab (monoclonal antibody against CD52 antigen present on mature T lymphocytes) and fingolimod (sphongosine-1-phosphate receptor modulator on the lymphocytes) are currently underway.

Treatment of CIDP

CIDP is a treatable disease, and previous trials have shown the efficacy of immunomodulatory agents compared to placebo in improving disability. These agents include corticosteroids [47], intravenous immunoglobulin (IVIG) [48, 49], and plasmapheresis (PE). Steroids or IVIG can be used as first-line therapy, although the authors favor the former as a first trial. A nonresponse to either therapy does not preclude the response to the other, and a switch from steroids to IVIG or vice versa should be considered when a patient fails to respond to a first-line therapy [50]. In one study, participants treated with IVIG improved by 54 % compared to 21 % in the placebo group. Long-term treatments including steroid-sparing immunomodulating agents such as methotrexate, cyclosporine, cyclophosphamide, and azathioprine have also been used successfully.

15.1.5 Multifocal Motor Neuropathy

15.1.5.1 Clinical Presentation

Multifocal motor neuropathy commonly presents in men and women (men > women, ~2:1) in the age group of 30–50 [51–54]. It affects about 1 in 100,000 persons, with male predominance (male:female, 2.6:1). While in most cases, it presents with an insidious, subacute onset, in some, it presents with an abrupt onset. Predominantly, distal segments of individual peripheral nerves are affected, both in the arm and the leg, although the arms are more affected, typically in an asymmetric fashion (Fig. 15.3). It is not uncommon to see subsegmental involvement of the individual nerves, for example, wrist extension versus finger extension. Although atrophy of the affected muscles is commonly noted, upper motor neuron signs are seldom seen (one of the most common clinical mimics of amyotrophic lateral sclerosis). Sensory

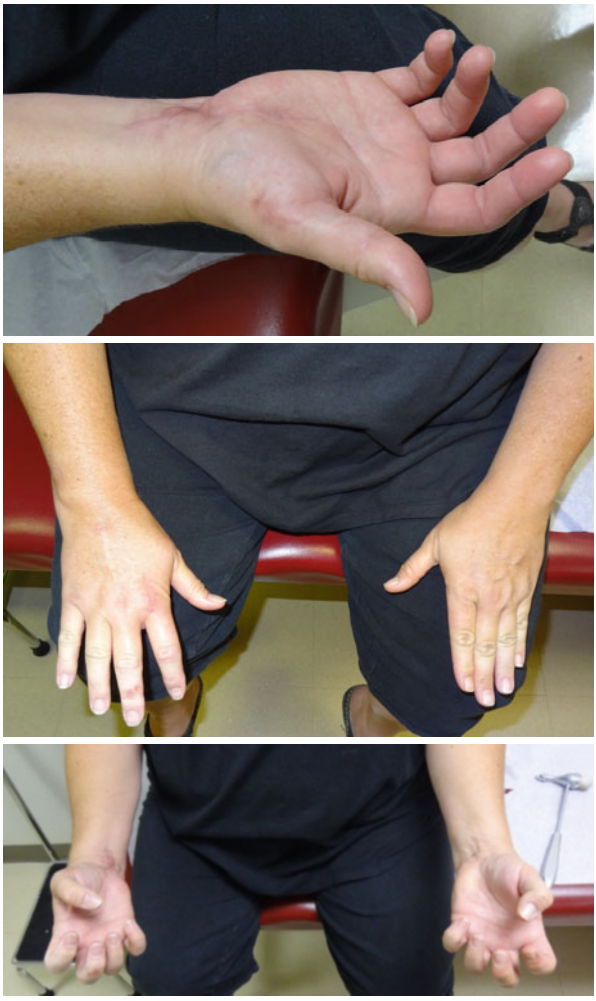


Fig. 15.3 MMN physical characteristics demonstrating subsegmental involvement. Shown are pictures of a patient with multifocal motor neuropathy (MMN), affecting the ulnar nerve in the right hand. Note the involvement of the right ulnar nerve with the presence of "ulnar clawing of hands" (*top*), inability to adduct fingers (due to weakness of dorsal interossei and palmar interossei muscles) (*middle*), and sparing of ulnar-innervated deep finger flexors (flexor digitorum profundus IV&V) (*bottom*)

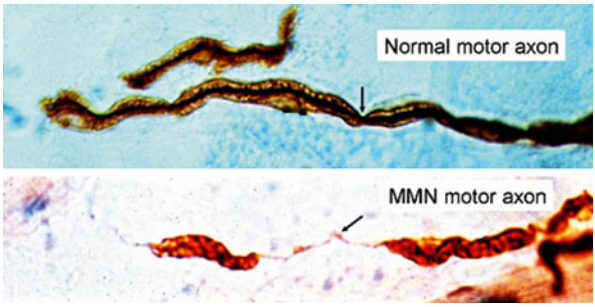


Fig. 15.4 Segmental demyelination (MMN). Shown are teased fiber preparations of nerves from a normal control (*top*) and a patient with multifocal motor neuropathy (*bottom*) demonstrating segmental demyelination of the axon. Picture courtesy of Dr. Alan Pestronk, MD, obtained with permission (http://neuromuscular.wustl.edu)

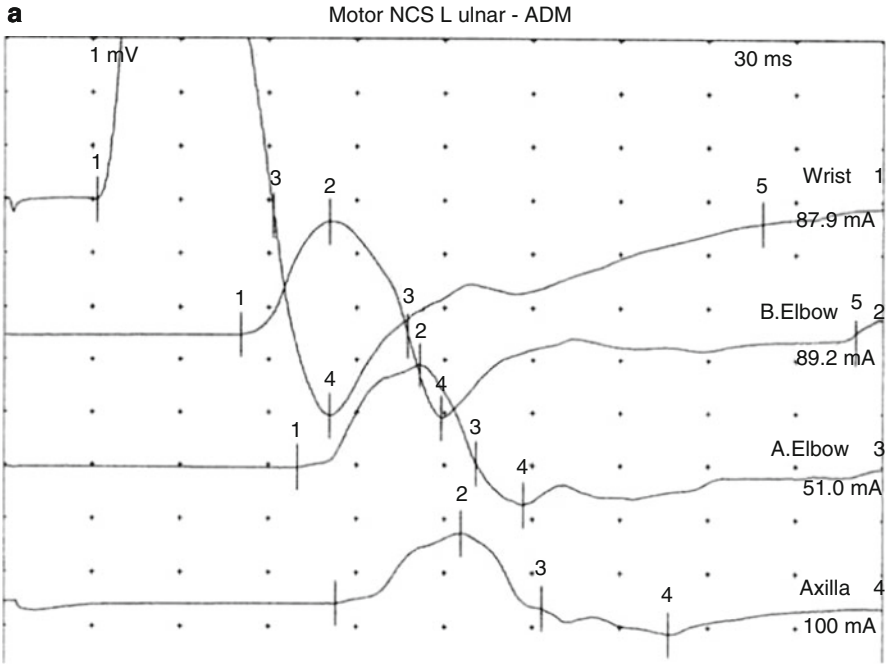
symptoms are minimal, if any, however, decreased vibration sensation may be noted in few cases. Spontaneous remissions are rarely seen. Acute worsening of clinical symptoms, in the setting of steroid treatment, is classic. IgM against ganglioside GM1 is noted in 50–80 % of the patients, depending on the report. It should be noted that, accordingly, IgM antibodies against GM1 are not specific to MMN, and they occur in other immune motor neuropathies as well. In addition, antibodies against other epitopes (such as NS6S and NP-9) have been noted in MMN. Although advances have been made in understanding this clinical syndrome, the exact pathophysiology remains unclear. Nerve biopsies show segmental demyelination (Fig. 15.4), axonal loss, and rare perivascular inflammation. Depolarization at the site of conduction block, hyperpolarization at sites distal to the conduction block, and activity-induced conduction blocks (due to dysfunction of various channels – sodium channels and sodium/potassium pump) have been described.

15.1.5.2 Electrodiagnostic Features

The classical electrodiagnostic hallmark of multifocal motor neuropathy is motor conduction block (Fig. 15.5a, b). Most of the times, the conduction block is noted distally. However, in a few number of cases, a proximal conduction block (between Erb's point and axilla) may be noted. Sensory studies and conduction velocities are usually normal; however, sensory potential amplitudes may be reduced without obvious sensory deficit [55, 56]. As opposed to conduction block with temporal dispersion that is noted commonly in AIDP/CIDP, conduction block associated with MMN does not show significant temporal dispersion. Mildly prolonged distal motor latencies may be occasionally encountered. Distal denervation of the innervated muscles and thoracic paraspinal denervation are commonly noted. In addition, electromyography may disclose fasciculations and myokymias.

15.1.5.3 Diagnosis

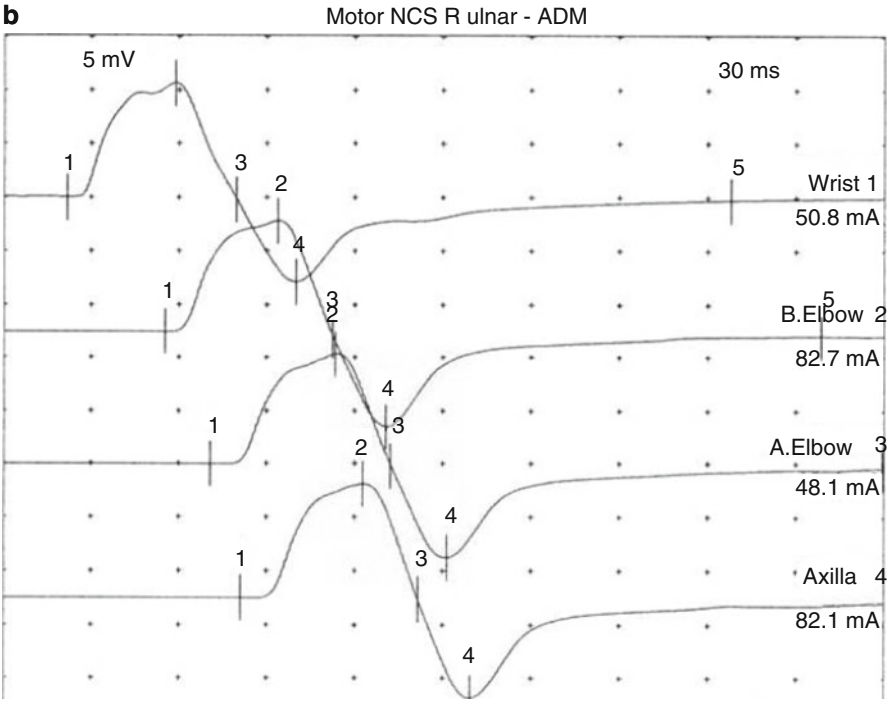
Nerve biopsy is not essential for diagnosis of MMN. The diagnosis of MMN is based on the EFNS criteria as has been described by Van Schaik et al. [57] and relies on clinical (1), electrodiagnostic (2), and supportive criteria (3) listed below.



Nerve/site	Recording site	Latency (ms)	Amplitude (mV)	Distance (cm)	Velocity (m/s)
Right ulnar - ADM					
Wrist	ADM	3.18 (3.5)	10.5 (5.0)	7	
Below elbow	ADM	8.07	**2.1**	21	**42.9** (50)
Above elbow	ADM	10.00	**2.0**	10	51.9
Axilla	ADM	11.30	**1.3**	7	53.8

Fig. 15.5 (**a**, **b**) Conduction block in MMN. (**a**) Shown is a sample trace of left ulnar motor nerve conduction study in a patient with MMN, *whose left side is unaffected*. Note the normal distal latencies, normal amplitude, no conduction block, and normal conduction velocities. The normal values for the nerve conduction study are noted within parentheses in the table. (**b**) Shown is a sample trace of right ulnar motor nerve conduction study in a patient with MMN, whose right side is affected. Note the normal distal latencies, normal distal CMAP amplitude, conduction block in the forearm segment, mildly slowed distal conduction velocities, and normal proximal conduction velocities. No temporal dispersion was noted. The normal values for the nerve conduction study are noted within parentheses in the table. The ulnar sensory studies were normal bilaterally (data not shown). Based on this study and other data (not shown), the conduction block can be localized to the ulnar nerve in the forearm segment distal to the branch to the flexor digitorum profundus (IV & V)

b



Nerve/site	Recording site	Latency (ms)	Amplitude (mV)	Distance (cm)	Velocity (m/s)
Left ulnar - ADM					
Wrist	ADM	2.19 (3.5)	10.7 (5.0)	7	
Below elbow	ADM	5.52	10.4	20.5	61.5 (50)
Above elbow	ADM	7.08	10.4	9	57.6
Axilla	ADM	8.13	10.6	7	67.2

Fig. 15.5 (continued)

1. Clinical criteria for multifocal motor neuropathy Van Schaik et al. [57] → EFNS criteria, modified from [58]:
   Core criteria (both must be present):
   - Slowly progressive or stepwise progressive, focal, asymmetric limb weakness (more than 1 MRC grade difference), that is, motor involvement in the motor nerve distribution of at least two nerves, for more than 1 month. If symptoms and signs are present only in the distribution of one nerve, only a possible diagnosis can be made.
   - No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs.

   Supportive clinical criteria:
   - Predominant upper limb involvement
   - Decreased or absent tendon reflexes in the affected limb

- Absence of cranial nerve involvement (rare exception of 12th cranial nerve)
- Cramps and fasciculations in the affected limb
- Response in terms of disability or muscle strength to immunomodulatory treatment

Exclusion criteria:

- Upper motor neuron signs
- Marked bulbar involvement
- Sensory impairment more marked than minor vibration loss in the lower limbs
- Diffuse symmetric weakness during the initial weeks

2. Electrophysiological criteria for conduction block (CB)

Definite motor CB:

- Negative peak CMAP area reduction on proximal versus distal stimulation of at least 50 % whatever the nerve segment length (median, ulnar, and peroneal). Negative peak CMAP amplitude on stimulation of the distal part of the segment with motor CB must be >20 % of the lower limit of normal and >1 mV, and increase of proximal to distal negative peak CMAP duration must be 30 %.

Probable motor CB:

- Negative peak CMAP area reduction of at least 30 % over a long segment (e.g., wrist to elbow or elbow to axilla) of an upper limb nerve with increase of proximal to distal negative peak CMAP duration of 30 %
- Negative peak CMAP area reduction of at least 50 % (same as definite) with an increase of proximal to distal negative peak CMAP duration >30 %

Normal sensory nerve conduction in upper limb segments with CB.

Evidence for CB must be found at sites distinct from common entrapment or compression syndromes.

3. Supportive criteria

Elevated IgM anti-ganglioside GM1 antibodies

Laboratory: increased CSF protein (<1 g/L)

Magnetic resonance imaging showing increased signal intensity on T2-weighted imaging associated with diffuse nerve swelling of the brachial plexus

Objective clinical improvement following intravenous immunoglobulin treatment

4. Diagnostic categories

(a) *Definite multifocal motor neuropathy* (after appropriate exclusions):

- Both the clinical core criteria, definite conduction block, and normal sensory studies

(b) *Probable multifocal motor neuropathy* (after appropriate exclusions):

- Both the clinical core criteria, probable conduction block in two nerves, and normal sensory studies

OR

- Both the clinical core criteria, probable conduction block in one nerve, normal sensory studies, and at least two supportive criteria

(c) *Possible multifocal motor neuropathy:* (after appropriate exclusions)

- Both the clinical core criteria, normal sensory studies, and objective clinical improvement

Clinical core criteria #1 (in one nerve), clinical core criteria #2, normal sensory studies, and either definite or probable conduction block in one nerve

15.1.5.4 Treatment

IVIG has been shown to be the mainstay of treatment. The clinical response to treatment is best when conduction block is present, and the disease duration has been shorter (or in the early phase of the disease). Cyclophosphamide has been found to be successful in patients with low GM1 titers. There is growing evidence that rituximab is helpful in treating MMN as well.

15.1.6 Other Selected Dysimmune Neuropathies

15.1.6.1 Anti-Hu Neuropathy Syndrome

Although sensory neuronopathies secondary to anti-Hu antibody syndrome [59–61] are more commonly seen, sensory, sensorimotor, autonomic, or motor or mixed variants are also seen. It is more commonly seen in females (80 % in the USA), middle-to-old age (39–83 years old). Ninety-five percent of the affected patients have a smoking history. Sensory loss, painful paresthesias, and dysesthesias are commonly noted. The initial involvement may be proximal or distal or proximodistal, either in a symmetric or an asymmetric fashion. Usually, both upper and lower extremities are affected, and proprioceptive defects, ataxia, and athetosis/pseudoathetosis are commonly seen. Coincident weakness can also be seen in selected cases. The presence of anti-Hu antibodies can lead to a variety of symptoms/presentations such as limbic encephalitis, cerebellar ataxia, autonomic dysfunction, Lambert-Eaton myasthenic syndrome, myelitis, or brainstem encephalitis. The most common associated neoplasm with the anti-Hu syndrome is small cell lung cancer. Rarely, other cancer types such as prostate small cell cancer, lung adenocarcinoma, gynecological cancers, or Hodgkin's lymphoma may be seen in association.

Electrodiagnostic studies show diffusely absent sensory responses or severely reduced sensory nerve action potentials [60]. Reduction in motor amplitudes may be seen; however, usually denervating changes such as fibrillations, positive sharp waves, and fasciculation potentials are not seen. CSF evaluation may suggest elevated white blood cell count (about 50 % of the cases) and elevated protein levels [62]. Pathological evaluation suggests involvement of the dorsal root ganglion, nonspecific inflammation of the brain/spinal cord, and axonal loss and of the posterior columns.

The treatment of this condition is arduous. The main treatment approach relies on treatment of the underlying primary tumor. Usually, the neurological symptoms do not get better; however, physical therapy may be helpful in managing sensory ataxia. Serial anti-Hu antibody levels are not very helpful in clinical management, although they show a decreased following excision of tumor.

15.1.6.2 Sjogren's Associated Neuropathy

The most common form of Sjogren's associated neuropathy is small fiber neuropathy, characterized by a burning sensation in the toes and fingers, decreased temperature sensation, normal strength, normal reflexes, and normal nerve conduction studies. However, similar to anti-Hu syndrome, pure sensory neuropathy or sensorimotor neuropathy or autonomic neuropathy may be seen. Steroids are helpful in treatment, at least in early stages.

15.1.6.3 Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes (POEMS)

This neuropathy evolves in a subacute fashion with involvement of the sensory and motor components. On nerve conduction studies, either demyelination or axonal changes may be noted. The patients are usually older, with prior diagnosis of monoclonal gammopathy of unknown significance (MGUS). Osteosclerotic lesions may be noted in progression of the disease. VEGF levels are found to be elevated in conjunction. Treatment relies on treatment of the underlying myeloproliferative disorder, including autologous bone marrow/stem cell transplants.

The other rarer forms of dysimmune neuropathies [63–75] and clinical summaries are presented in Table 15.2.

15.2 Summary

Acquired immune-mediated neuropathies are commonly seen in neuromuscular clinics. Clinical history and course, examination, electrodiagnostic findings, histopathological, CSF, laboratory, and serological evaluations can help differentiate from hereditary neuropathies and classify the subtype/variant based on specific patterns of involvement. The right subtype evaluation is critical since the treatment modalities differ within the subtypes. IVIG, steroids, and other immunomodulators are helping in managing these acquired neuropathies. However, some forms remain recalcitrant to treatment. The pathophysiology underlying the immune-mediated neuropathies is beginning to be understood. Our understanding of the intricacies of the pathophysiology may lead to novel treatments in the future.

Table 15.2 Summary of other dysimmune neuropathies

Antibody to:	Clinical presentation	Laboratory evaluation	NCS	Response to treatment
Contactin 1 antigen or Contactin 1/ Contactin-associated protein 1 (paranodal antigens)	Age of onset is more advanced compared to typical CIDP (71 vs. 51.6 years, respectively) Distal or diffuse weakness, sensory disturbances, and gait ataxia	IgG anti-contactin 1 antigen	Demyelination, evidence of conduction block and evidence of axonal loss with active denervation	Mainly prednisone Poor or partial response to HIG Partial response given the evidence of axonal damage
Neurofascin (Member of the L1 subgroup of adhesion molecules expressed at the nodes of Ranvier (NF186) and the paranodes (NF155) in both the CNS and PNS)	Associated with CNS and PNS demyelinating disease Patients with CIDP have IgG4 antibody against NF155 in paranodal segment Chronic or rapidly progressive weakness, predominantly distal, sensory disturbances, ataxia, and disabling low-frequency postural and intention tremor	IgG4 anti-Neurofascin antigen	Demyelinating neuropathy	Poor response to prednisone and HIG Partial response to plasmapheresis
CNS myelin antigen (CMA): GALOP syndrome Gait disorder Autoantibody Late onset Polyneuropathy	Patients have disabling gait with sensory ataxia and frequent falls In general, slowly progressive (over years) distal more than proximal, pan-modal sensory neuropathy/motor neuropathy	Antibody: IgM against CNS myelin antigen (CMA)	Heterogeneous electrodiagnostic studies: demyelinating (with no block or temporal dispersion) or axonal neuropathy	HIG Cyclophosphamide

(continued)

Table 15.2 (continued)

Antibody to:	Clinical presentation	Laboratory evaluation	NCS	Response to treatment
Sulfatide: major acidic glycosphingolipid in central and peripheral nerve myelin	Chronic, distal, sensory>motor neuropathy, predominantly demyelinating, associated with axonal loss, with ataxia in 50 % of cases Could be associated also with Guillain-Barre syndrome, small fiber neuropathy	Monoclonal gammopathy (IgM) IgM anti-sulfatide antibody	Demyelinating and axonal features	HIG Cyclophosphamide Plasmapheresis
POEMS Polyneuropathy Organomegaly Endocrinopathy Monoclonal gammopathy *S*kin changes	Symmetric, sensory, and motor neuropathy To be suspected when a patient with CIDP diagnosis is not responding to standard CIDP therapy.	Elevation in plasma and serum levels of VEGF (*level correlates with disease activity*). IL-1β, IL-6, TNF-α also increased. Monoclonal gammopathy (almost always lambda) Production of almost always lambda light chain Osteosclerotic lesions (95 % of cases)	Evidence of demyelination and axonal sensorimotor neuropathy, with no conduction block	Radiation therapy Chemotherapy (i.e., melphalan, cyclophosphamide, thalidomide, lenalidomide, etc.) Autologous stem cell transplantation
GM2 and GalNac-GD1a ganglioside	Chronic sensory ataxia with mild distal motor involvement	IgM Kappa paraprotein IgM anti-GM2 and GalNac-GD1a antibody	Demyelinating features (slow conduction velocity, prolonged distal latency, and conduction block) Axonal loss could be seen	HIG

Sjogren syndrome-related neuropathy: spectrum of manifestation	1. *Painful small fiber neuropathy (most common)*: painful distal paresthesias		1. Normal electrodiagnostic studies. Decrease intraepidermal nerve fiber density	Corticosteroid/HIG
	2. *Sensory/motor/autonomic neuropathy*			
	3. *Sensory neuronopathy:* sensory ataxia secondary to involvement of dorsal root ganglia. Can be associated with autonomic dysfunction including Adie's pupils, orthostatic hypotension, hypohidrosis, or anhidrosis	3. Lymphocytic infiltration on dorsal root ganglia biopsy	3. Absent sensory responses with preserved motor responses on NCS	
	4. *Mononeuritis multiplex*	4. Vasculitis of small arteries or arterioles on sural nerve biopsy and subsequent axonopathy		
	5. *Demyelinating neuropathy*			
	6. *Cranial neuropathy*: mainly trigeminal neuropathy. Other affected cranial nerves include III, VI, VII, IX, X	6. Possible vasculitis of small arteries and arterioles		
	7. Carpal tunnel syndrome			
CANOMAD: Chronic ataxic neuropathy Ophthalmoplegia Ig*M* paraprotein Cold *A*gglutinin Disialosyl Antibodies	Chronic sensory ataxia Motor and sensory involvement of cranial nerves including external ophthalmoplegia, dysarthria, dysphagia	Anti-disialosyl IgM paraprotein with cross-reactivity to GD2, GD3, GD1b, GT1b, GT1a, GQ1b	Absence of sensory responses on NCS Normal or mildly reduced amplitudes of motor responses on NCS Demyelinating features are present in 50 % of cases	No randomized trial available Plasmapheresis, HIG, or other immunomodulatory agents

CIDP chronic inflammatory demyelinating polyneuropathy, *HIG* human immune globulin, *CNS* central nervous system, *PNS* peripheral nervous system, *VEGF* vascular endothelial growth factor, *NCS* nerve conduction study

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Amyotrophic Lateral Sclerosis: Epidemiology and Risk Factors

16

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16.1 Introduction

Amyotrophic lateral sclerosis (ALS) is the most common degenerative disorder of motor neurons. The disease determines progressive paralysis of voluntary muscles, which ultimately ends in death, usually from respiratory failure, after a median time of 2.5 years after symptom onset [1]. ALS patients have been traditionally distinguished into familial (FALS) or sporadic (SALS) based on family history. FALS cases represent 5–10 % of the total and are caused by mutations in >20 genes, most importantly *C9orf72*, *SOD1*, *TARDBP*, and *FUS*. Conversely, SALS cases are believed to be determined by a complex and still largely unknown interplay between genetic and environmental risk factors [2]. However, the distinction between FALS and SALS is somewhat artificial for several reasons. First, the definition of FALS is not unequivocally accepted [3]. Second, the overlap between FALS and monogenic ALS is only partial. In fact, the occurrence of ALS phenocopies in a single family can be explained by shared environmental exposure or by chance alone. On the other hand, a considerable number of SALS cases carry pathogenic mutations in known ALS genes, further blurring the distinction between the two forms of the disease [2]. Lastly, it is well recognized that ALS and some forms of frontotemporal dementia (FTD) belong to the same disease spectrum, sharing common genetic, pathologic, and pathogenic features. Specific genetic defects can result in both ALS and FTD, often co-occurring in the same kindred. As such, an apparently sporadic case of ALS with a positive family history for FTD should rather be considered as an instance of a more complex familial neurodegenerative disease. In fact, ALS

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patients have a higher-than-expected frequency of other neurodegenerative diseases among relatives, supporting the notion of a genetically driven susceptibility to neurodegeneration [2].

The clinical hallmark of ALS is the presence of signs of degeneration of both upper and lower motor neurons (UMNs and LMNs, respectively) in multiple body regions. UMN loss determines spasticity and brisk deep tendon reflexes, whereas LMN loss determines muscle atrophy, weakness, and fasciculations. The disease starts in one region and then spreads, usually with a contiguous pattern and a linear progression. In about three-quarters of cases, ALS begins in a limb, whereas in 20 %, and more commonly in females and with advancing age, it has bulbar onset with dysarthria and dysphagia. Rarely, respiratory or trunk muscles are first affected [1].

Median survival of ALS patients is 30 months. Fifteen to twenty percent of patients are alive at 5 years and 5–10 % survive longer than 10 years. Long-term survivors are usually patients with younger onset and prevalence of UMN impairment [1]. In fact, age at onset is a strong prognostic factor in ALS, showing an inverse relationship with survival. Site of onset is another important predictor of survival, bulbar and respiratory onset being associated with a shorter survival. Other negative prognostic factors are early involvement of respiratory muscles and rate of reduction of functional vital capacity, rate of muscle strength loss and rate of decline in functional status, poor nutritional status (expressed by low body mass index), and cognitive impairment [4].

16.2 Epidemiology

Data about ALS epidemiology largely derive from studies conducted among populations of European descent. Incidence and prevalence of ALS are similar in Europe and North America [5]. A 2010 large epidemiological study examining six population-based registries of three European countries (Ireland, the UK, and Italy) for the 2-year period 1998–1999, covering as many as 24 million individuals, estimated ALS incidence in Europe as 2.16/100,000 persons/year. Within the population aged 18 years or older, the annual incidence was 3 for men and 2.4 for women. The male/female ratio was 1.4:1. Data were similar among the six registries, implying that the epidemiology of ALS in Europe is the same among populations of different ethnic background (Celtic, Anglo-Saxon, and Mediterranean). A notable exception was the higher incidence of bulbar-onset disease in Ireland as compared to the other European populations examined [6]. According to a recent systematic review of the global epidemiology of ALS, the prevalence of ALS in Europe is 5.4/100,000 [7]. The lifetime risk of developing ALS is 1:350 for men and 1:400 for women [5].

In Italy, according to an epidemiological study performed on data collected between 1995 and 2004, ALS has an incidence of 2.64/100,000 persons/year, which has been stable over time. The male/female ratio is 1.28:1. Prevalence is 7.89/100,000 [8]. Southern Italy does not differ from the rest of the country and from Europe with

respect to ALS incidence and prevalence [9]. In Sardinia, an increase in ALS incidence and prevalence has been observed over the last four decades. ALS in Sardinia may represent a specific disease entity because of the genetically isolated nature of the Sardinian population and because a significant number of cases carry pathogenic mutations in *TARDBP* or *C9orf72* [10].

Similar figures have been observed in North America. For instance, in western Washington State, ALS incidence is 2.1/100,000 persons/year among males and 1.9 among females [11]. A 2014 study indicated a nationwide prevalence of ALS in the United States of 3.9 cases/100,000. The disease is more common among white males, non-Hispanics, and people aged 60–69 years [12].

ALS incidence increases with age, especially after 40 years, reaching a peak at 70–74 years for men and 65–69 years for women and then declining thereafter. Cases over 80 years represent only 6.6 % of the incident population, and cases older than 85 years represent 1.9 % [6]. Several factors could partly explain this finding apart from a real biological decline in susceptibility to the disease: diagnostic difficulties in the elderly due to atypical phenotypes and comorbid conditions; reduced referral of elderly patients to diagnostic facilities; tendency to consider muscle wasting and weakness in this age group as manifestations of other more common non-neurological diseases or as consequences of ageing; shorter time from onset to death because of faster progression of the disease itself or because of demise due to other comorbid diseases, so that death occurs before diagnosis is reached; and the will not to make such a dismal diagnosis in an elderly patient in order to preserve serenity in the final stages of life.

ALS is more common in men than in women, with a male/female ratio of 1.5:1 [13]. The main reason for this disproportion is the higher frequency of spinal-onset disease in men, which is twofold more common than in women, especially in the 70–80 age group [6].

According to a 2001 systematic review, incidence of ALS has increased by 46 % in Europe and North America between 1960 and 1990, from 1.3 to 1.9/100,000/year. This trend seems to have been driven by Southern European countries, where a 162 % increase in incidence has been observed, in comparison to a smaller increase in North America and Northern Europe. Moreover, incidence has risen in females more than in males, and the total increase is largely attributable to that observed in people aged 75 years or older, while the change was smaller in people aged 25–74 years. Data concerning changes in prevalence are less certain, but there appears to be an increase as well. The main explanation for the increased incidence of ALS over the decades is the expanded life expectancy, but other factors should also be considered, namely, increased recognition, diagnosis, and registration of the disease [14].

ALS is less common among non-Caucasian populations. In these ethnic groups, the annual incidence is almost invariably less than 1/100,000 [15]. Higher rates, similar to those observed in Europe and North America, have been reported in Uruguay and Argentina, but this can be explained by the fact that in those countries the wide majority of the population is of European ancestry [16, 17]. In North America, African Americans, American Indians, and Alaska Natives display lower

incidence than Caucasian inhabitants [18, 19]. Japan has an ALS incidence for the age range 45–74 of 2/100,000/year, which is lower than that of Caucasians [20]. China has a lower rate of 0.6/100,000/year [21], and Iran an even lower one of 0.42/100,000 [22]. A study of ALS mortality in the mixed population of Cuba found that mortality rate was similar to that of the Hispanic population of the United States, suggesting that genetic admixture could be a factor protecting against the disease [23].

When viewing at lower incidence rates of ALS in non-Caucasian contexts, however, reduced life expectancy should be taken into account: for example, in Libya an annual incidence of 0.87/100,000 has been reported, but in that country 81 % of the population is younger than 40 years, so that adjusted incidence for the age range 45–74 gives an annual rate of 4.6/100,000, which is similar to that observed in Europe and North America [24]. This indicates that shorter life expectancy in developing countries is a factor that partly contributes to reduced incidence of the disease in those countries.

Some geographical clusters of ALS have been described in the past decades, the most widely known being the island of Guam in the Western Pacific and Kii Peninsula in Japan [5]. In the 1940s an unusually high occurrence of both ALS and a syndrome of parkinsonism and dementia (parkinsonism-dementia complex, PDC) was reported in the indigenous Chamorro population of Guam, reaching an annual incidence of 273 cases/100,000 in Umatac village. Both conditions showed familial aggregation; moreover, they often occurred together in the same individuals or in the same kindreds and were both characterized neuropathologically by tau neurofibrillary tangles. In the following decades, incidence of Guamanian ALS-PDC decreased but still remained higher than in the rest of the world. Several factors have been advocated to explain the syndrome, none of which has been firmly established. The most credited theory is the so-called cycad hypothesis, which implies a neurotoxic role for the non-proteinogenic amino acid beta-methylamino-L-alanine (BMAA). This is produced by cyanobacteria living in symbiosis with *Cycas circinalis*, a plant whose seeds were usually eaten by the Chamorros. A related theory hypothesized that pathogenic BMAA was acquired through dietary consumption of fruit bats which fed on cycad seeds, thus amplifying the amount of toxin [25]. Importantly, very recent work has demonstrated that mutations in genes responsible for established neurodegenerative diseases, namely, *PINK1*, *DCTN1*, *FUS*, and *HTT*, contribute to the excess incidence of neurodegeneration in Guam kindreds [26].

In the 1950s an unusually high incidence of ALS, up to 150 times higher than that of the remaining parts of Japan, was reported in two areas of the Kii Peninsula, namely, the southernmost part flanking the Koza River (towns of Kozagawa and Kushimoto) and Hohara district. Similar to Guam, familial clustering and association with parkinsonism and dementia often occurred, and tau neurofibrillary tangles were found at autopsy. The incidence of the disease decreased in the 1980s but still remained higher than in the rest of Japan. Several hypotheses have been made on the aetiology of Kii ALS: infectious agents, genetic defects, nutritional deficiencies, and toxic factors were considered. The main hypothesis, still undemonstrated, was centred on a dietary imbalance, with deficiency of calcium and magnesium and

relative excess of aluminium which was thought to be detrimental for neuronal function and survival [27]. In 2012 a genetic study demonstrated that 20 % of ALS patients in the southern focus of Kii carried the *C9orf72* expansion [28]. However, this genetic defect does not account for the majority of ALS cases in Kii, for which other factors necessarily play a role.

16.3 Risk Factors

To date, no environmental risk factor has been unequivocally defined for ALS. The only established risk factors are positive family history, male gender, and ageing. Research into environmental risk factors for ALS is intricate for several reasons. First, the range of possible exposures spans the entire lifetime of an individual and thousands of physical and chemical agents. Second, investigations in this field are time and resource consuming and results are not guaranteed. Third, genetic factors may alter the impact of environmental ones and thus hamper their recognition. Finally, studies on environmental influences are often flawed by methodological failings [5]. In the following sections the main risk factors that have been suggested to contribute to ALS pathogenesis are briefly discussed.

16.3.1 Cigarette Smoking

Cigarette smoking is likely the most convincing exogenous risk factor for ALS, even though not all studies agree. A 2009 review of existing evidence by Armon stated that smoking could be considered as an established risk factor for ALS [29]. In their 2009 prospective study, Gallo and colleagues examined the EPIC cohort consisting of 517,890 healthy persons followed up for a total time of 4,591,325 person-years. They found that current smokers had a double risk of developing ALS compared to never smokers, while former smokers at the time of enrolment had a 50 % increase in risk. The number of years of smoking was proportional to the risk of ALS, and the time elapsed since stopping smoking decreased the risk compared to persons continuing smoking. The authors concluded that their results strongly supported an etiopathogenic role of smoking in ALS and hypothesized that this could be explained by lipid peroxidation due to exposure to formaldehyde [30]. However, most other studies did not find a dose-response relationship between smoking and risk of ALS. A 2010 meta-analysis concluded that smoking is a risk factor for ALS only among females [31].

16.3.2 Military Service

The hypothesis that military service may be associated with ALS was raised by reports of increased incidence, hospitalization, and/or mortality rates for ALS among veterans deployed to the Persian Gulf War of 1990–1991. According to the

work of Horner and colleagues, the relative risk of developing ALS for the deployed military personnel as a whole was 1.92, and a similarly increased risk was demonstrated for active-duty military, air force, and army personnel, whereas a trend toward increased risk was seen for Reserves, National Guard, Navy, and Marine Corps [32]. Such evidence prompted the US Institute of Medicine (IOM) to review the topic, and in 2006 a report was published by the IOM stating that there was "limited and suggestive evidence of an association between military service and later development of ALS" [33].

In 2005 Weisskopf and coworkers published a prospective study analysing for ALS mortality in the period 1989–1998 over 500,000 US men participating in the Cancer Prevention Study II cohort of the American Cancer Society. An increased ALS mortality was noted among those who had served in the military with respect to those who had not (RR 1.53). Importantly, the risk was elevated in every 5-year birth group from 1915 to 1939. This implies that the increase in ALS risk is not unique to deployment in the Gulf War but must depend on some other factor linked to military service such as exposure to insecticides or other chemicals, inhalation of aerosolized lead, traumatic injuries, viral infections, or heavy physical activity [34]. A 2015 review concluded that an association between military service and ALS seems to exist but available evidence is too limited to draw firm conclusions, and at present there is no definite proof of a link between a specific military exposure and ALS [35].

16.3.3 Physical Activity

The attention toward physical activity as a risk factor for ALS originally came from the personal stories of some well-known sportsmen who developed the disease, the first and most famous being the baseball player Lou Gehrig, as well as from the clinical impression, shared by many neurologists, that ALS patients frequently report propensity to physical exertion in their previous healthy life and display a lean and athletic body constitution [2]. In fact, this impression is supported by epidemiological evidence. In a 2002 case-control study, Scarmeas and coworkers found that slimness and previous varsity athletic activity conferred an odds ratio of developing ALS of 2.1 and 1.7, respectively [36]. More intriguingly, Mattsson et al. showed that physical fitness, but not muscle strength, was associated with risk of ALS, and the authors interpreted this finding as compatible with the concept that physical activity is not per se a risk factor for the disease, but both physical fitness and development of ALS are promoted by an underlying constitutional predisposition [37]. This hypothesis is supported by the work of Huisman and colleagues, who in 2013 demonstrated that ALS is associated with leisure time physical activity but not with work-related physical activity nor with physically intense sports, and no dose-response relationship exists between level of physical activity and risk of developing the disease [38]. In agreement with this view are the findings that a healthier cardiovascular profile and lower body fat and body mass index (BMI) are associated with ALS [39].

An alternative interpretation of such findings, however, could be that individuals with a favourable cardiovascular profile have a higher chance of developing ALS

because they are less likely to die from other more common diseases [5]. Finally, a recent large epidemiological research has given somewhat surprising results regarding physical activity and risk of ALS. The authors of this European case-control study analysed 652 patients and 1166 controls in the time period 2008–2012, and they concluded that physical activity is not associated with ALS; on the contrary, it seems to exert a protective role against the disease. The authors hypothesized that physical exercise activates some cellular mechanisms protecting motor neurons against degeneration [40].

16.3.4 Soccer

It has been hypothesized that Italian professional soccer players are at increased risk for ALS. The first impulse to this view came from an inquiry started in 1999 by an Italian public prosecutor about the causes of death of Italian soccer players and the alleged use of illicit substances during their active career. The inquiry examined about 24,000 professional players of the three main categories active between 1960 and 1997 and found that 8 of them had died of ALS, a number about tenfold higher than expected based on Italian incidence rates [5]. Two years later Chiò and coworkers published a study on 7,325 players of the two top series active between 1970 and 2001, obtaining a 6.5 standardized mortality ratio (SMR) for ALS (5 observed cases as opposed to 0.77 expected). Therefore the authors concluded that being an Italian professional soccer player conferred a strong risk of developing ALS [41]. Another study by Taioli found an SMR of 18.18 in Italian players for the period 1975–2003 [42]. Several factors have been advocated to explain the apparently marked increase in risk linked to soccer: repeated trauma (whether head trauma or peripheral one), physical exercise, drugs (especially NSAIDs), nutritional supplements (branched-chain amino acids, vitamins, minerals), and use of pesticides on football pitches [43].

However, the above epidemiological investigations have been criticized as flawed by methodological failings, the main of which is represented by an underestimation of the expected mortality from ALS. According to those criticisms, if correct mortality estimations had been obtained, no excess risk for ALS among Italian football players would have resulted [44]. On the basis of these counterarguments, a 2013 review on the subject concluded that the association between football and ALS cannot be confirmed. However, it seems reasonable to conclude that ALS in soccer players may display some phenotypical peculiarities, most importantly earlier age at onset than in the general population [43]. The link between ALS and soccer has not been extensively studied in countries other than Italy.

16.3.5 Metals and Chemicals

A 2009 review of existing literature examined 50 studies on exposure to metals and 38 studies on exposure to chemicals with relation to ALS risk. The metals considered were lead, mercury, aluminium, cadmium, chromium, manganese, and

selenium. No association was found between exposure to any metal and development of ALS. The chemicals examined belonged to three categories: organic solvents, agricultural chemicals, and pesticides. An association of ALS risk with pesticides was evidenced [45]. A 2012 meta-analysis confirmed this association and pointed in particular to the category of organochlorine insecticides [46].

16.3.6 Occupation

A meta-analysis about occupation and risk of ALS was conducted in 2009 on 12 studies reporting risk estimates for individual occupations. Six categories of potentially relevant occupations were identified: veterinarians and other health-care workers, athletes, hairdressers, power-production plant personnel, electrical workers, and military personnel. However, detection of associations was hampered by methodological limitations of the study, and the review concluded that more rigorous studies with precise assessment of occupation were needed to draw firm conclusions about occupational risk of ALS [47].

16.3.7 Cyanotoxins

Following the observation of the increased incidence of ALS in Guam, a role for BMAA produced by cyanobacteria has been hypothesized in ALS etiopathogenesis. Actually, cyanobacteria are found in every terrestrial and aquatic habitat, and their toxins can enter the body via several routes such as drinking or other contact with water, aerosolization, or consumption of contaminated fish or plant foods; therefore, their role in ALS development could not be limited to the Guamanian form of the disease [48]. For example, a cluster of ALS cases has been described near Lake Mascoma in New Hampshire, in which cyanobacteria algal blooms had been reported [49]. However, current evidence does not allow to establish firm conclusions about a causal role of cyanotoxins in ALS outside Guam [50].

16.3.8 Other Risk Factors

Other risk factors have been proposed for ALS but supporting evidence is less consistent in comparison to previously discussed associations. Among these factors are: electrical injury and exposure to electromagnetic fields, head trauma, viruses, statins, dietary factors, melanoma, autoimmune diseases, and geographical clustering other than that observed in Guam and Kii [50].

Conclusions

The causes of sporadic ALS, which is the most common form of the disease, are as yet unknown. Although environmental factors are likely to be involved, no one has been unequivocally implicated in ALS pathogenesis yet. This can be

attributed at least in part to methodological difficulties that are intrinsic to epidemiological studies on environmental influences.

In the near future additional epidemiological researches are needed on larger cohorts of patients in order to better define the role played by the environment in ALS development and progression. Moreover, it is likely that the interplay between genetic and environmental factors may trigger and/or promote neurodegeneration, and future studies should be designed to capture this phenomenon. This could represent an important step forward in the way of deciphering the still largely obscure field of ALS etiopathogenesis.

Key Points

- ALS is a neurodegenerative disease of motor neurons and causes progressive paralysis of voluntary muscles and death.
- ALS has a prevalence of 6/100,000 and an annual incidence of 2/100,000; incidence increases with ageing and is higher in Caucasians and in males.
- 90 % of ALS cases are sporadic, likely due to the interplay between genetic and environmental risk factors.
- The only certain risk factors for ALS are positive family history, male gender, and advancing age.
- Proposed environmental risk factors for ALS include cigarette smoking and other exposures (physical activity, military service, pesticide exposure, etc.) for which the epidemiological evidence is still conflicting.

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Paraneoplastic Diseases of the Peripheral Nervous System

17

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17.1 Introduction

Peripheral nervous system involvement is the most commonly observed condition in patients with paraneoplastic neurological syndromes (PNS), and its clinical manifestations are highly heterogeneous. The peripheral nervous system can be variously involved, but the most frequently affected sites are the dorsal ganglia and presynaptic nerve endings of the neuromuscular junction. While peripheral nervous system damage can be induced by various mechanisms in patients with systemic malignancy, in patients with paraneoplastic neuropathy, it is usually of autoimmune origin and only rarely associated with direct tumour infiltration or caused by chemotherapy. Metabolic-related causes are also uncommon. PNS arise in less than 1 % of patients with malignancy, preceding the diagnosis of cancer by months or even years in the majority of cases [38]. Specific serological markers can be used to screen for classical paraneoplastic syndromes, as defined by Graus et al. [2, 19]. Subacute sensory neuropathy and Lambert-Eaton myasthenic syndrome (LEMS) are classified as classical syndromes. Onconeural antibodies directed against neural antigens expressed by the tumour may occur in most affected patients, suggesting an underlying autoimmune process [16].

The disorders are presented here below according to peripheral nervous system site (Table 17.1).

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Table 17.1 Paraneoplastic diseases of the peripheral nervous system and muscles

Peripheral nerves	Subacute sensory neuronopathy
	Monoclonal gammopathy and neuropathy
	Paraneoplastic vasculitic neuropathy
	Paraneoplastic dysautonomic neuropathy
	Unusual paraneoplastic neuropathy
	Acquired neuromyotonia
Neuromuscular junction	Lambert-Eaton myasthenic syndrome
Muscle	Dermatomyositis/polymyositis
	Other myopathies

17.2 Description and Discussion of the Topic

17.2.1 Peripheral Nerves

17.2.1.1 Subacute Sensory Neuronopathy (SSN)

Subacute sensory neuronopathy, first described by Denny-Brown in 1948 [10], results from lymphocyte-induced destruction of sensory neurons in the dorsal root ganglia. It is characterised by subacute, rapidly progressive onset, with chiefly multifocal or asymmetrical sensory loss, symptoms of paraesthesia and pain and, typically, upper limb involvement, extending in some cases to the face, chest, or abdomen. Sensory loss, most markedly affecting deep sensation, leads in many cases to severe sensory ataxia of the four limbs. Although very disabling, subacute sensory neuronopathy has been reported to have an indolent clinical course [18].

SSN is the hallmark characteristic in over 50 % of patients with paraneoplastic encephalomyelitis (PEM). Most patients with SSN also present signs and symptoms suggestive of multifocal limbic, cerebellar, brainstem, or spinal cord involvement [9, 18].

The cardinal feature of paraneoplastic SSN is a marked loss of primary, most notably large-diameter sensory neurons in the dorsal root ganglia, following a diffuse but patchy, asymmetric pattern. Signs of nonspecific degenerative changes are present in the remaining neurons. Infiltration by T and B lymphocytes, plasma cells, and macrophages varies considerably and often shows perivascular distribution. Myelinated fibres are severely depleted in the dorsal columns, posterior nerve roots, and peripheral sensory nerves, believed to be secondary to the loss of dorsal root [12].

Cerebrospinal fluid (CSF) is usually altered (with raised protein, mild mononuclear pleocytosis, elevated IgG index, and/or oligoclonal bands) but is reported to be normal in at least 10 % of patients. At electrophysiology, sensory nerve potentials are characteristically absent or severely diminished in amplitude, with normal or only slightly reduced sensory nerve conduction velocities, when a response can be elicited. Some electrophysiological abnormalities in motor nerve conduction are observed in the majority of patients, with or without symptoms of mixed sensorimotor polyneuropathy, but motor nerve is almost always less impaired than sensory

nerve conduction. Needle EMG may show denervation in patients with a motor neuropathy or encephalomyelitis component and anterior horn cell involvement. Sural nerve biopsy reveals nonspecific axonal degeneration and a decrease in myelinated fibres [7, 36].

Patients usually have severe sensory deficits, areflexia, and sensory gait ataxia, which must be considered in the differential diagnosis of paraneoplastic SSN. In the absence of a known malignancy, the differential diagnosis of sensory neuronopathy or severe sensory neuropathy includes dorsal root ganglionitis associated with Sjogren's syndrome, idiopathic sensory neuronopathy, and sensory neuropathy associated with anti-disialosyl ganglioside antibodies. In the presence of a known cancer diagnosis, the differential diagnosis also includes cisplatin- or paclitaxel-induced sensory neuropathy.

Although SSN is associated with various tumours, small-cell lung cancer accounts for 70–80 % of cases [18].

Most patients harbour anti-Hu antibodies, which show 99 % specificity and 82 % sensitivity for the diagnosis of cancer in patients with suspected SSN [16]. Anti-Hu antibodies stain the nuclei and, to a lesser degree, the cytoplasm of all neurons in the dorsal root ganglia, autonomic ganglia, and central nervous system. They react with a group of closely related 35–40 kD RNA-binding proteins, several of which have been cloned. Expression of one or more Hu autoantigens is frequent but not universal among small-cell lung carcinomas, including tumours of patients with SSN/PEM and anti-Hu antibodies and tumours of patients with no neurological symptoms.

A small number of patients with SSN/PEM associated with small-cell lung carcinoma or with another malignancy either have no detectable anti-neuronal autoantibodies or harbour antibodies with patterns of immunoreactivity that differ from anti-Hu antibodies (Table 17.2). These include anti-CV2 (CRMP-5) antibodies targeted against a group of proteins expressed by neurons and oligodendrocytes, anti-amphiphysin antibodies, and anti-Ma antibodies. The clinical features of SSN/PEM in anti-Hu-antibody-negative patients do not reliably differ from the spectrum of signs and symptoms seen in patients with anti-Hu antibodies. Anti-Hu or other anti-neuronal antibodies in patients with sensory neuronopathy are a robust (but not absolute) marker of an underlying tumour. Nevertheless, a paraneoplastic condition and an occult neoplasm may be present even in the absence of anti-neuronal antibodies.

Table 17.2 Onconeural antibodies in paraneoplastic neuropathies

Onconeuronal antibody	Associated tumour(s)	Antibody reactivity and antigen specificity
Anti-Hu (ANNA-1)	Small-cell lung carcinoma	Pan-neuronal nuclei > cytoplasm; 35–40 kD RNA-binding proteins
Anti-CV2 (CRMP-5)	Small-cell lung carcinoma, others	Cytoplasm of neurons and oligodendrocytes; 66 kD CV2 protein
Anti-amphiphysin	Small-cell lung carcinoma	Neuropil; synaptic vesicle-associated amphiphysin
Anti-Ma	Lung, testis, and other carcinomas	Pan-neuronal nuclei and nucleoli; 37 kD Ma1 and 40 kD Ma2 proteins

Despite being the most common symptom of the anti-Hu syndrome, subacute sensory neuronopathy has been isolated in only 24 % of patients, while the others have various combinations of central and peripheral nervous system involvement.

17.2.1.2 Monoclonal Gammopathy and Neuropathy

Neuropathies associated with monoclonal gammopathy may in some cases be of paraneoplastic origin. Monoclonal gammopathy may underscore or transform into a haematological malignancy on whose treatment neurological improvement often depends [32]. The neuropathy associated with malignant monoclonal gammopathy requires further investigation in the presence of IgM gammopathy to exclude Waldenström's macroglobulinaemia or other lymphomas [29]. Peripheral neuropathy causes complications in as many as 20 % of patients with Waldenström's macroglobulinaemia [14], and the IgMs may be directed at the myelin sheath [30]. Solitary plasmacytoma, multiple myeloma, or polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) should be considered in patients with IgG or IgA monoclonal gammopathy. Peripheral neuropathy at the time of diagnosis is uncommon in patients with multiple myeloma, and neuropathies are often secondary to the use of neurotoxic drugs (e.g. thalidomide and bortezomib) [15]. POEMS or Crow-Fukase syndrome is a rare plasma cell condition with multiorgan involvement. Its aetiology is not yet known, but there is an increasing body of evidence that vascular endothelial growth factor (VEGF) may play a role. Diagnosis continues to be based on both clinical findings and guidelines [11] since there are no specific tests or pathognomonic signs. POEMS syndrome targets in particular peripheral nerves, and neuropathic symptoms dominate the clinical picture [41]. It is frequently misdiagnosed as CIDP due to its prominent features of demyelination and axonal degeneration. The associated monoclonal gammopathy is generally IgG or IgA, often carrying a lambda light chain. Correct diagnosis is critically dependent on the concurrent presence of systemic symptoms/signs (including organomegaly, endocrinopathy, pleural effusions, ascites, peripheral oedema, Castleman's disease, sclerotic bone lesions, thrombocytosis, skin changes, papilloedema) and increased levels of serum VEGF. Early treatment is crucial. First-line therapy in patients with dominant sclerotic plasmacytoma includes radiation of the lesion. Systemic therapy is indicated for patients with diffuse disease [1, 11, 24, 33]. Clinical response to treatment is associated with VEGF levels [11, 41, 48].

17.2.1.3 Paraneoplastic Vasculitic Neuropathy

Peripheral nerve microvasculitis may be associated with lymphomas or carcinoma of the lung, prostate, uterus, kidney, or stomach [27, 35]. Neurological symptoms usually precede diagnosis of the tumour. The disorder usually presents as mononeuritis multiplex or asymmetric distal sensorimotor neuropathy. Pain is frequently reported. Patients' sedimentation rate is usually high, but cutaneous vasculitis or other systemic symptoms are rarely present. Clinical involvement is asymmetric as shown in nerve conduction studies by varying levels of motor and sensory axonal degeneration. Sural nerve biopsy or autopsy demonstrates focal mononuclear cell infiltration of epineurial vessel walls and active nerve fibre degeneration. Additionally arteriolar fibrinoid

necrosis may be present with obliteration of lumens. Patients with peripheral nerve vasculitis and small-cell lung cancer may also present clinical and pathological features of SSN/PEM [35, 46]. Patients with small-cell lung cancer may harbour anti-Hu antibodies, with or without overt central nervous system (CNS) involvement [13]. Neurological symptoms have been reported to improve after tumour treatment and/or cyclophosphamide; corticosteroids alone do not seem to be effective.

17.2.1.4 Paraneoplastic Dysautonomic Neuropathy

Dysautonomia may be considered to be an isolated paraneoplastic peripheral neuropathy in a minority of patients. Chronic pseudo-obstruction is the most common syndrome. Symptoms may include severe, progressive gastrointestinal dysmotility, as gastroparesis, chronic intestinal pseudo-obstruction, and severe constipation/obstipation, preceding detection of the small-cell lung carcinoma by several months [9, 18]. The majority of patients do, however, develop dysautonomia alongside another paraneoplastic syndrome (mostly sensory neuronopathy), and the association with lung tumours, especially small-cell lung carcinoma, and Hu antibodies is robust [31]. Dysautonomic paraneoplastic syndrome is believed to be underdiagnosed insofar as it develops in the context of at least one other paraneoplastic syndrome which likely dominates the presentation, masking the autonomic features. The syndrome responds only rarely to tumour treatment, and no case studies have been conducted with immunotherapy.

17.2.1.5 Unusual Paraneoplastic Neuropathies

Some controversy still surrounds the possible relationship between Guillain-Barré syndrome (GBS) and cancer, and the existence of a paraneoplastic form of GBS has not been confirmed. The cases with malignancies are usually clinically similar to the other cases of GBS [44], and eighteen patients in the PNS Euronetwork database (unpublished reports) have been diagnosed with GBS or CIDP and a tumour. Interestingly, several patients had both Hu antibodies and signs of demyelination on electromyography. These cases are most likely rare variants of Hu antibody-associated neuropathies.

Still more intriguing are the cases of sensorimotor neuropathy and malignancy in the absence of onconeural antibodies. Graus et al. [19] classifies these as possible PNS, if a tumour is detected within 3 years. To classify these cases as paraneoplastic, further investigation is needed: firstly, to rule out any pre-existing neuropathies or carcinomatous neuropathy associated with severe illness and/or weight loss and, secondly, bearing in mind that some tumours, as multiple myeloma, may give rise to several types of peripheral neuropathy.

17.2.1.6 Acquired Neuromyotonia

Neuromyotonia (NMT) is a generalised peripheral nerve hyperexcitability disorder. The characteristic clinical picture is of muscle stiffness, twitching (fasciculations) and/or rippling (clinical myokymia), painful cramps, impaired muscle contraction or pseudomyotonia, and muscle weakness. Muscle hypertrophy can develop. The limb or limb and trunk muscles are most frequently affected [26]. Some 33 % of patients also have sensory symptoms and approximately 50 % develop

hyperhidrosis. Central nervous system features (as hallucinosis, insomnia, chorea) could be present and, in its florid form, may be referred to as Morvan's syndrome. EMG reveals neuromyotonic and or myokymic discharge.

Neuromyotonia is paraneoplastic in around 25 % of cases (5–10 % in the Euronetwork database) and can precede the discovery of a tumour by up to 4 years. The most frequently associated tumours are thymoma with or without myasthenia gravis, small-cell lung cancer, and haematological malignancies. Anti-voltage-gated potassium channel (anti-VGKC) antibodies are usually associated with these syndromes and are found in about 35 % of all PNH patients and in as many as 80 % in the presence of thymoma. They do not, however, differentiate the paraneoplastic from the non-paraneoplastic form [25].

17.2.2 Neuromuscular Junction

17.2.2.1 Lambert-Eaton Myasthenic Syndrome (LEMS)

LEMS is a presynaptic disorder of the cholinergic neuromuscular and autonomic synapses. It is paraneoplastic in 60 % of cases and usually associated with small-cell lung cancer [37]. Muscle weakness is the predominant feature in the proximal lower limbs and can extend to other skeletal muscles, including the eye muscles. Respiratory failure is uncommon and tendon reflexes are depressed or abolished. Autonomic dysfunction is characterised by mouth or eye dryness, blurred vision, impotence, constipation, impaired sweating, or orthostatic hypotension [49].

Repetitive nerve stimulation usually shows low compound muscle action potentials after nerve stimulation, with decrement at low-frequency stimulation and increment of over 100 % after high-frequency stimulation or brief maximal effort. In a minority of patients, LEMS is associated with paraneoplastic cerebellar degeneration [8].

This syndrome, be it paraneoplastic or not, depends on antibodies directed to P/Q-type voltage-gated calcium channels (VGCC) [50].

17.2.3 Differential Diagnosis

Several other types of neuropathies are often considered to be paraneoplastic. It is important to emphasise that 30 % of neuropathies in persons aged over 50 years are cryptogenic [45]. Extensive workup rarely reveals the diagnosis. Several neuropathy entities are discussed in more detail below.

17.2.3.1 Inflammatory Neuropathies

The relationship between inflammatory neuropathies, as GBS and CIDP, and tumours is controversial. There seems to be a preponderance towards lymphomas (NHL and HD) [6], but there are no definite characteristics or markers. From the acute forms, the varieties of the paraparetic form need to be considered [47]. Several CIDP subgroups have been observed in association with cancer [4].

In general, inflammatory neuropathies, be they acute or chronic, do not appear to have a primarily paraneoplastic cause.

17.2.3.2 Vasculitis

The question of paraneoplastic vasculitis has been discussed in recent years, and individual cases have been reported [28, 51]. Vasculitic neuropathies are not included in the diagnostic criteria of paraneoplastic neurological diseases [19]. The current recommendation is that the presentation of vasculitic neuropathy likely has a heterogeneous autoimmune mechanism, which may have been triggered by drugs in individual cases, but does not have a cancer-related cause.

17.2.3.3 Neoplastic Neuropathies

Depending on the cancer site, several different types of peripheral nerve involvement exist, all of which are rare.

1. Meningeal spread: In rare cases, meningeal spread can mimic peripheral neuropathy. Severe meningeal carcinomatosis can affect multiple roots and resemble neuropathy. Rarely, isolated infiltration of the cauda equina can produce flaccid paraparesis, which is usually associated with pain, some asymmetry, and cranial nerve and CNS involvement.
2. Infiltration of peripheral nerves by cancer can be widespread and occur in a neuropathy-like lesion, can affect individual parts of peripheral nerves and the plexus, and can also spread along peripheral nerves. Anastomosis between cranial nerves can also be the target of cancer infiltration [21].
3. Symmetric involvement of peripheral nerves mimicking polyneuropathy is almost exclusively observed in lymphoma and leukaemia [22]. In lymphoma in particular, the term neurolymphomatosis is used, in addition to the intravascular type [20, 39, 42]. Several reports have suggested that neurolymphomatosis can mimic CIDP [23].

Solid tumours, as other types of cancer, can compress and spread locally, but do not invade nerves in a generalised way.

17.2.3.4 Paraproteinaemic Neuropathies

Paraproteinaemic neuropathies are usually considered to be an entity of their own. The clinician is usually confronted with monoclonal gammopathy of undetermined significance (MGUS, e.g. a neuropathy with anti-MAG antibodies), sometimes in association with myelin-associated glycoprotein (MAG). Several types of more specific neuropathies are observed in multiple myeloma, Waldenström's disease, and in some types of non-Hodgkin's lymphoma and Castleman's disease.

In addition to this complex aetiology, neuropathies do not manifest homogeneously but represent a spectrum ranging from axonal to demyelinating forms.

Whether paraproteinaemic neuropathies deserve to be classified as "paraneoplastic" or need to be placed in a more distinct group, due to their more tangible cause-effect relationship, remains to be decided [5].

17.2.3.5 Chemotherapy-Induced Neuropathy (CIPN)

In patients being treated for cancer, neuropathies are usually caused by therapy. In addition to the cumulative toxicities observed with vinca alkaloids, taxanes, platinum drugs, bortezomib, and thalidomide [3], several other paradigms need to be considered.

(a) Acute effects: Effects are observed with oxaliplatin [40], and taxanes can in some cases produce immediate effects. In addition to acute effects, oxaliplatin also produces cumulative toxicity. A new class of drugs, delivering neurotoxicity by targeted antibodies, as brentuximab vedotin or adotrastuzumab emtansine, are under evaluation.
(b) Late effects: There are increasing reports of the late effects of chemotherapy [34]. These manifest in persisting neuropathic symptoms as pain and Raynaud's syndrome.
(c) Autoimmune effects: Autoimmune diseases and inflammatory neuropathies have appeared in therapies with immune checkpoint inhibitors.
(d) Role of pre-existing neuropathies: The role of pre-existing neuropathies in the expression of CIPN is still controversial. Several types of genetic neuropathies seem to increase the risk of developing CIPN [43].
(e) Mimics: In addition to the differential diagnosis, the clinician must also be aware of local cauda compression, acute myopathies, and electrolyte disorders.

Conclusions

Peripheral nerves are a common target for paraneoplastic attack. There is a clear predominance of subacute sensory neuronopathy (SSN) with well-established clinical features and oncological and immunological associations. However, the association between onconeural antibodies and a specific clinical picture and outcome remains to be demonstrated. In addition, no randomised clinical trials have been conducted on the treatment of SSN, and it is general (but not evidence-based) opinion that the best treatment opportunity for these cases is through early tumour detection [17].

LEMS is an autoimmune disorder of paraneoplastic and non-paraneoplastic origin. LEMS patients should thus be screened not only for voltage-gated calcium channel (VGCC) but also for onconeural antibodies, especially if they are VGCC-antibody-negative.

In the presence of a neuropathy associated with a monoclonal gammopathy, a combined neurological and haematological approach is recommended to exclude any underlying malignancies. IgM MGUS neuropathies are mainly demyelinating, more sensory than motor in character, slowly progressive, and often associated with anti-MAG antibodies. The underlying tumour may be Waldenström's macroglobulinaemia. The neuropathies associated with IgG or IgA MGUS present with a CIDP-like course, but multiple myeloma, solitary plasmacytoma, and POEMS should be ruled out. Treatment depends on both the severity of the neuropathy and the haematological condition.

Poor prognosis is the hallmark of patients with paraneoplastic dysautonomia, probably because they fail to respond to immunotherapy and seldom improve with cancer treatment. This may reflect the underlying neuronal death, as suggested by robust associations with Hu antibodies and small-cell lung cancer. Nevertheless, nearly 40 % of SSN – in the presence of DRG cell loss – and 30 % of other neuropathies with similar antibody and tumour profiles improve after tumour therapy. This remarkable response rate challenges the received wisdom that PNS associated with neuron loss is rarely treatable and should prompt further studies on the mechanisms and best management of these disorders.

Finally, further studies are warranted (a) to better characterise the relationship between sensorimotor neuropathies and malignancies after ruling out all potential confounding conditions related to treatment toxicity and (b) to better characterise the oncological profile of patients with paraneoplastic neuropathies in addition to the consolidated relationship with small-cell lung cancer.

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Diabetic Neuropathy

18

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18.1 Definition

Diabetic peripheral neuropathy (DPN) is defined as the presence of peripheral nerve dysfunction in people with diabetes mellitus (DM) after the exclusion of other causes of neuropathy [1].

18.2 Epidemiology

DM is by far the most common cause of neuropathy. Prevalence estimates may vary depending on differences in inclusion criteria; approximately 54 % of patients with type 1 DM (T1DM) and 45 % with type 2 DM (T2DM) disclose symptoms and/or signs of neuropathy [2]; DPN is present in up to 10 % of patients at the time of diagnosis and up to 50 % after 20 years history of diabetes.

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Duration and severity of hyperglycaemia represent modifiable risk factors for the development of neuropathy: indeed, enhanced glycaemic control was shown to reduce the prevalence of clinical neuropathy by 60–70 % in T1DM [3] and by 7 % in T2DM [4].

Diabetes is a clear risk factor for nondiabetic neuropathies; for example, the incidence of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is 11-folds higher in diabetic patients than in nondiabetic individuals.

The link between prediabetes (impaired fasting glucose or impaired glucose tolerance (IGT) [5] needs further scientific proofs; indeed, the prevalence of "idiopathic peripheral neuropathy" was found to be three times higher in IGT than in normal age-matched controls [6]. Additional studies are ongoing in order to identify modifiable risk factors within the metabolic syndrome that may influence the development and progression of DPN [5].

18.3 Clinical Subtypes

DPN encompasses all patterns of neuropathy (Table 18.1) with significant overlaps and combinations between different clinical subtypes.

Distal symmetrical polyneuropathy (DSP). DSP is the most common syndrome [7]. It may become symptomatic several years after the onset of T1DM or it may reveal an underlying T2DM. DSP may be entirely asymptomatic despite of minimal signs and clear electrophysiological changes.

DSP is a length-dependent neuropathy dominated by sensory disturbances with stocking-glove distribution: early symptoms begin in the toes and extend over the feet; in more progressed cases the sensory loss extends above the knees and involve the fingers, hands and forearms; eventually, sensation over the anterior chest and abdomen may become also affected due to involvement of the shorter sensory axons in intercostal nerves. Motor impairment is usually minor and is mainly distributed in the distal lower-limb muscles.

The syndromic spectrum of DSP varies accordingly the prevalent involvement of the large or small fibres. In the large-fibre variant, the neuropathy manifests with painless paraesthesias, impairment of light touch sensation, sensibility to pressure and vibration and joint position sense and with diminished stretch reflexes. Large-fibre DSP may result in increased instability with sensory ataxia and positive Romberg's sign; however, the severest diabetic pseudotabes picture (loss of joint sensations, severe lancinating pain and pupillary abnormalities) is uncommon nowadays.

Small-fibre neuropathy (SFN) is increasingly recognized as an early manifestation of DSP. New SFN cases are often associated with prediabetes. Selective SFN is a "pseudo-syringomyelic" neuropathy which spares the large-fibre functions. SFN manifests with spontaneous pain and diminished thermal and pain perception. Severest SFN results into painless burns, persistent foot ulcers and neuropathic osteoarthropathy and is often accompanied by prominent autonomic neuropathy.

Diabetic autonomic neuropathy (DAN) is usually associated with predominant SFN; it may range from subclinical functional impairment of cardiovascular reflexes

Table 18.1 Clinical patterns of diabetic neuropathy and differential diagnoses

Diabetic neuropathy	Differential diagnosis*
Symmetrical neuropathies	
Distal symmetrical polyneuropathy	Vitamin B12 deficiency. Alcohol. Chemotherapy. CIDP. Monoclonal gammopathies
Small-fibre neuropathy	Idiopathic. Connective tissue diseases. Vitamin B12 deficiency. Monoclonal gammopathies. HIV infection. HCV infection. Celiac disease. Chemotherapy
Diabetic autonomic neuropathy	Hereditary or haematological amyloidosis. Sjögren syndrome. Immune-mediated autonomic neuropathies (anti-ganglionic AchR antibodies). Paraneoplastic neuropathies (anti-Hu antibodies; anti-PAC2 antibodies). HSAN
Symmetrical, episodic painful neuropathies	
Treatment-induced neuropathy	
Diabetic neuropathic cachexia	
Asymmetrical focal/multifocal neuropathies	
Limb mononeuropathies	Other compression/entrapment neuropathies
Mononeuritis multiplex	Systemic or nonsystemic vasculitides. Peripheral neurolymphomatosis
Proximal motor (or radiculoplexopathy, or diabetic amyotrophy, or Bruns-Garland syndrome)	Systemic or nonsystemic vasculitides. Neoplastic or infectious polyradiculoneuropathies. Radiation-induced plexopathy. Compressive radiculopathies. Spinal stenosis. Idiopathic plexopathies
Truncal neuropathy	Intrathoracic, intra-abdominal or intraspinal diseases. Herpes zoster
Cranial neuropathies	Compressive cranial neuropathies

*Note that up to 10 % of cases of peripheral neuropathy in diabetic patients is not related directly to DM. Since the diagnosis of diabetic peripheral neuropathy requires the exclusion of other causes, clinically convergent neuropathies should be considered and ruled out. CIDP and neuropathies related to vitamin B12 deficiency, hypothyroidism and uraemia also occur more frequently in diabetic patients than in nondiabetic; metformin is associated with higher risk of vitamin B12 deficiency with hyperhomocysteinaemia

CIDP chronic inflammatory demyelinating polyradiculoneuropathy, *Anti-PAC2* anti-type 2 Purkinje cell antibody, *HSAN* hereditary sensory autonomic neuropathy

and sudomotor function to overt symptoms and severe life-threatening complications. The incidence of DAN increases with patients' age, disease duration and poor glycemic control, but subclinical autonomic changes may occur within a year of diagnosis of T2DM and within 2 years in T1DM. Cardiovascular autonomic neuropathy (CAN) manifests with early resting tachycardia (due to early involvement of longest parasympathetic fibres), exercise intolerance and postural hypotension (with possible postural syncopes) which may be aggravated by diarrhoea or by tricyclic antidepressant used for pain treatment. Gastrointestinal dysfunction includes asymptomatic or symptomatic gastroparesis (which may concur to poor glycaemic

control inducing insulin-related hypoglycaemia), constipation or, rarely, explosive diarrhoea. Intensive insulin treatment may be complicated also by blunted sympathetic response to hypoglycaemia with unawareness of hypoglycaemia. Genitourinary dysfunction with impotence (erectile failure and retrograde ejaculation) is often the first manifestation of DAN in diabetic men (prevalence between 27 and 75 %); concurrent causative factors include vasculopathies and hormonal alterations. Urinary dysfunction due to bladder atony and impaired bladder sensation may lead to urine retention, dysuria, nocturia, incomplete bladder emptying and urgency up to overflow incontinence. Sudomotor abnormalities cause distal anhidrosis with skin's dryness, compensatory facial and truncal sweating and heat intolerance; gustatory sweating refers to profuse sweating in face and forehead immediately after food intake. Pupillary abnormalities such as sluggishly reactive pupils to light or Argyll Robertson-like pupils may be detected in up to 20 % of diabetic patients. Finally, reduced peripheral and central chemosensitivity to hypoxia and altered bronchomotor tone in lung may concur to explain the higher prevalence of sleep apnea syndrome in DM.

Episodic painful neuropathies are rare. *Treatment-induced neuropathy* develops with acute burning pain in the distal lower limbs in T1DM or T2DM patients after first achievement of tight glucose control by insulin ("insulin neuritis"), oral hypoglycaemic medications or severe dietary restriction. Pain has marked nocturnal exacerbations, may persist for weeks/months before spontaneous resolution and may affect areas such as the trunk and abdomen. Treatment-induced neuropathy is a usually length-dependent SFN often accompanied by autonomic dysfunction in the absence of relevant neurological signs besides hyperalgesia and allodynia. Proposed pathogenetic mechanisms include endoneurial ischaemia, hypoglycaemic microvascular neuronal damage and regenerating nerve firing. *Diabetic neuropathic cachexia* is an acute, severe, symmetrical, painful neuropathy with allodynia, associated with marked unintentional weight loss, depression, insomnia and impotence in males. The disorder may affect patients with T1DM or T2DM irrespectively of the duration of the disease. The condition is reversible over weeks to months after adequate diabetic control.

Limb mononeuropathy. Compression or entrapment neuropathies of the median, ulnar or peroneal nerves have an increased frequency in DM. Approximately a quarter of patients have electrophysiological signs of carpal tunnel syndrome (CTS) and 5–10 % are symptomatic for CTS. Rarer mononeuropathies with abrupt painful onset followed by weakness and atrophy are caused by nerve infarction from occlusion of *vasa nervorum*; the sequential involvement of two or more nerves is known as *mononeuritis multiplex*.

Lumbosacral radiculoplexopathy (LSRP). LSRP (alias diabetic amyotrophy or Bruns-Garland syndrome) affects the lumbosacral or more rarely the cervical plexus. LSRP is unrelated to the duration of disease or degree of glucose control and it may develop prior to diagnosis of T2DM in middle or old-aged men with concomitant weight loss. Onset is acute or subacute, with burning or lancinating pain in the back, hip or thigh, spreading to involve the entire limb; after days or weeks pain is followed by difficulty in walking and climbing stairs with wasting

and weakness of the quadriceps, iliopsoas, gluteus and, to a lesser extent, hamstring and anterior tibialis muscles; knee and ankle jerks are usually lost. In some cases the opposite leg may become affected after days or months. Progression may be steady or stepwise and may continue for months before the disease stabilizes. Up to 60 % of cases overlap with DSP and disclose a more gradual onset.

Truncal radiculopathy is usually unilateral, affects spinal roots from T4 through T12 and manifests with pain and dysaesthesias possibly associated with bulging of abdominal muscles and focal anhidrosis.

Cranial neuropathies. Acute unilateral oculomotor palsies affecting the third or sixth nerves are common; facial Bell's palsy also appears more common in diabetics than in nondiabetic individuals. The third nerve involvement is likely ischaemic since pathological cases disclosed a centrofascicular lesion in the intracavernous portion sparing the peripheral parasympathetic fibres [8]. Onset is abrupt and may be heralded or accompanied by transient pain in the frontal head or behind the affected eye; progression develops over 1–2 days and results into a nearly or fully complete dysfunction with diplopia, dysconjugate gaze and ptosis; pupillary reaction to light is typically (but not always) spared; spontaneous recover ensues within 2–3 months but relapses on the opposite sites can occur.

Six-month prognosis does not differ significantly from Bell's palsy in individuals without diabetes; treatment with steroids should be cautious.

Young patients with poorly controlled T1DM may develop a mild form of anterior ischaemic optic neuropathy.

18.4 Complications

Neuropathic pain occurs in up to 21 % of diabetic patients without a clear relation to age, diabetes duration, metabolic control or severity of neuropathy. Pain may develop in the absence of relevant clinically and neurophysiological findings and may be highly disabling leading to sleep disturbances, anxiety and significant functional limitations [9]. Pain is spontaneous, intermittent or continuous, and usually worse at night making uncomfortable the touch of feet against bedclothes. Pain is symmetrically localized in toes and may progress with a stocking-and-glove distribution; it is usually burning, electric or stabbing (but it may be aching and deep in the feet, especially on weight bearing) and associated to dysaesthesias, hyperalgesia and allodynia to light touch.

Acrodystrophic changes are a major complication of DSP-SFN. Calluses or phlyctenular lesions in feet usually precede the development of chronic ulcers which may develop in 4–10 % of patients (due to sensory loss, unnoticed traumatic tissue damage and vascular insufficiency) and may be complicated by chronic osteomyelitis. In some cases idiopathic bullae (*bullosis diabeticorum*) of hands may develop before plantar ulcers. *Neuropathic arthropathy* (diabetic Charcot foot) involves mainly the small joints with painless fractures of metatarsal bones, disruption or articular surfaces and disorganization of metatarsophalangeal joints.

Falls. Sensory ataxia and postural hypotension are major factors for increased risk of falls in diabetic patients together with retinopathy and vestibular dysfunction.

Cardiac mortality. Increased risk of mortality results from complications of CAN such as increased occurrence of asymptomatic ischaemia and impaired hypoglycaemic awareness, as well as from other diabetic complications such as coronary artery disease, stroke and diabetic nephropathy.

18.5 Pathology and Pathophysiology

The pathological process differs in different clinical subtypes.

DSP. Sural nerve biopsy (Fig. 18.1) discloses variable loss of myelinated fibres and unmyelinated fibres and axonal degeneration; there may be some degree of primary demyelination, proliferation of Schwann cells (SC) and onion-bulb

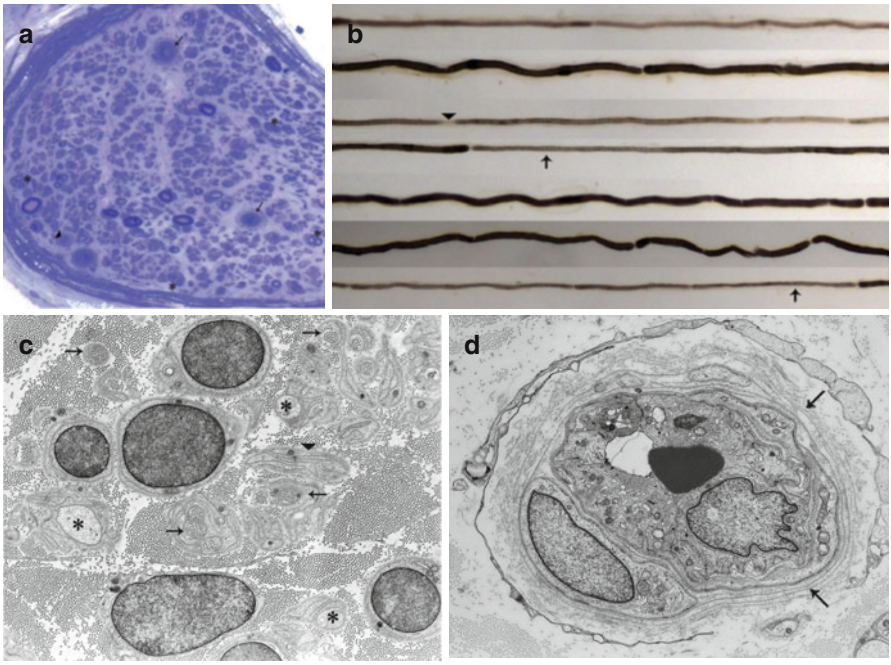

Fig. 18.1 Sural nerve biopsy from a patient with diabetic DSP. (**a**) Semithin section (original magnification 20×) showing loss of myelinated fibres, two endoneurial capillaries with thickened walls (*arrows*), some regenerative clusters made by small fibres (*asterisks*) and a small onion bulb indicative of repeated demyelination (*arrowhead*). (**b**) Teased fibres (original magnification 20×) showing contiguous portions of myelinated fibres with paranodal demyelination (*arrowhead*) and segmental remyelination (*arrows*). (**c**) Electron micrograph (transverse section, original magnification 4400×) showing severe loss of unmyelinated fibres with collagen pockets (*arrows*) and denervated Schwann cell processes (*arrowhead*); few unmyelinated fibres are identifiable (*asterisks*). (**d**) Electron micrograph (transverse section, original magnification 3000×) showing an endoneurial capillary with multiple layers of reduplicated basal lamina (*arrows*)

formation. Endoneurial capillaries show signs of microangiopathy with hyperplastic endothelial cells and thickening of the capillary wall and basal lamina. Dying-back centripetal axonal degeneration may be evident with regeneration subsequent to degeneration of the distal axons; fibre degeneration predominates distally correlating with diffuse abnormalities of nerve conduction velocities (NCV) with a proximo-distal gradient; this distal "dying-back" pattern is consistent with a metabolic disturbance. Loss of nerve fibres may be multifocal suggesting that microangiopathy also plays a causative role.

SFN. Skin biopsy reveals a selective reduction of thinly myelinated Aδ- and unmyelinated C-fibres. The morphometrical analysis of intraepidermal nerve fibres (IENF), a widely validated diagnostic method, demonstrates a reduction of unmyelinated sensory endings which represent the most distal nociceptors [10]. The loss of IENF occurs usually in a length-dependent manner as shown in skin from distal leg and thigh and may be associated with morphological abnormalities such as axon swellings, varicosities, branching and sprouting (Fig. 18.2). These abnormalities may be present early in the course of diabetic neuropathy and are considered

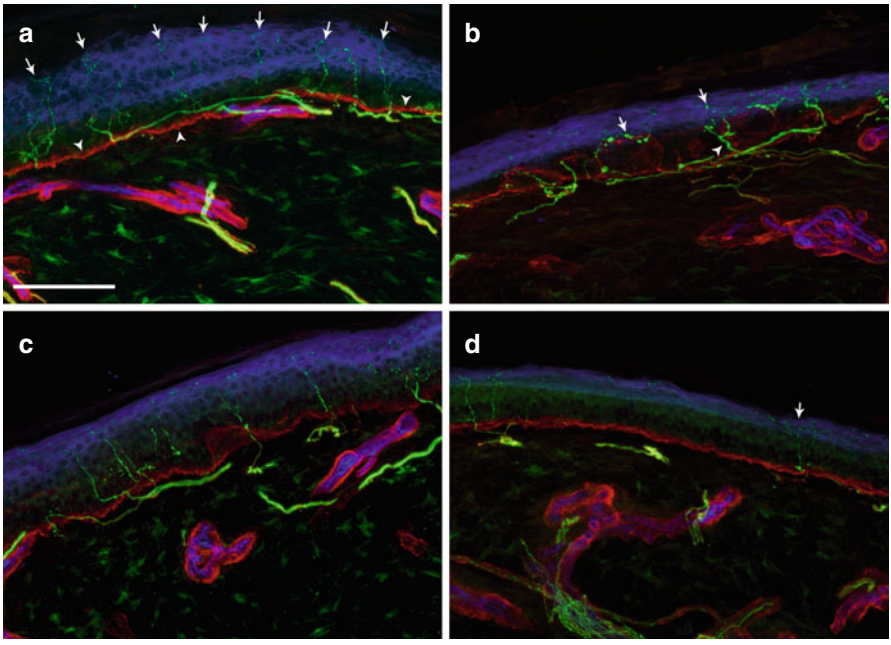

Fig. 18.2 Confocal images showing a length-dependent loss of intraepidermal nerve fibres in a diabetic patient (**b**, **d**) compared to a healthy control (**a**, **c**). Intraepidermal nerve fibres (IENF *arrows* in **a**) are regularly distributed with higher density in the proximal site (thigh, **a**) compared to the distal site (leg, **c**). In the diabetic patient there is a loss of IENF more severe in the distal site (**d** compared to **b**) with evidence of morphological abnormalities such as axon swellings (*arrowhead* in **b**), varicosities (*arrows* in **b**) and branching (*arrow* in **d**). Nerve fibres are in *green* (protein gene product 9.5); basal membranes and vessels are in *red* (collagen IV); epidermis and endothelia are in *blue* (*Ulex europaeus*, agglutinin). Scale bar = 100 μm

pre-degenerative changes [11]. New promising methods of analysis will provide an accurate quantitation of other nerve fibre subtypes such as autonomic dermal fibres to sweat glands, *arrector pilorum* muscles and vessels (Fig. 18.3); in diabetic neuropathy the depletion of autonomic fibres correlates with sweating impairment [12]. SFN can be also detected at the corneal level by in vivo corneal confocal microscopy (CCM) which analyses the density of both Aδ- and C-fibres of trigeminal origin;

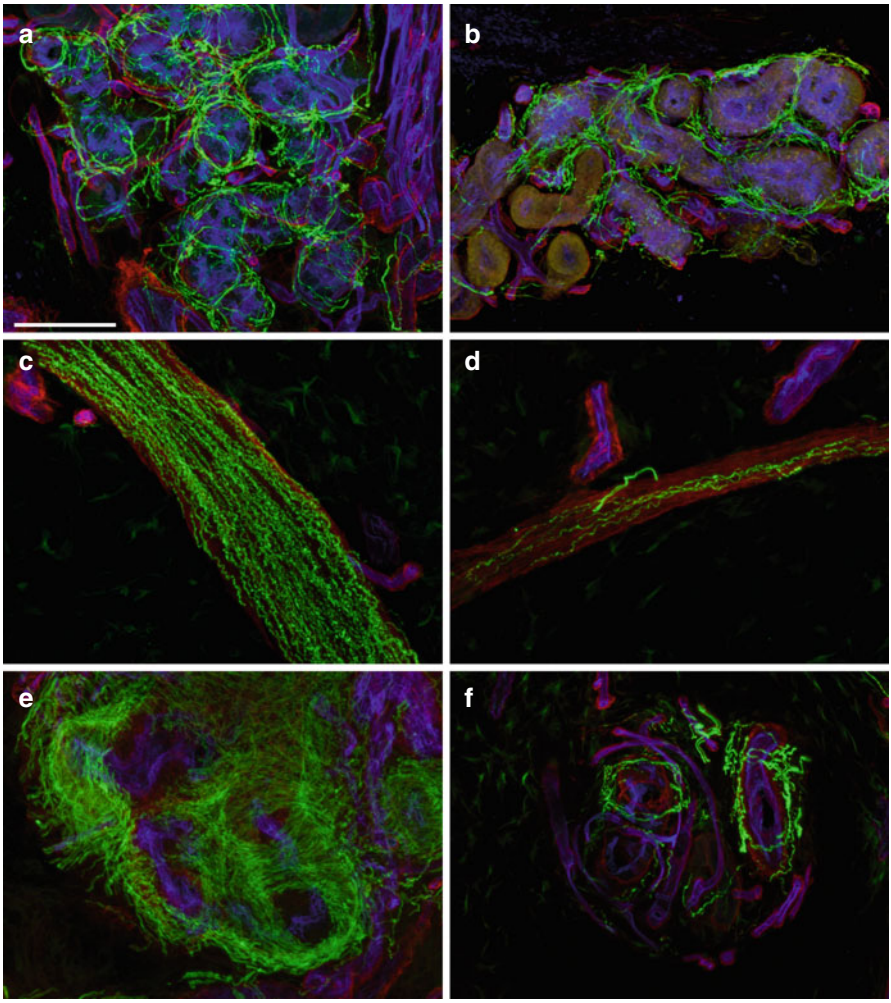

Fig. 18.3 Confocal images showing cutaneous autonomic innervation to sweat gland (**a**, **b**), arrector pili muscle (**c**, **d**) and arteriovenous anastomosis (**e**, **f**) in a healthy control (**a**, **c**, **e**) and in a diabetic patient (**b**, **d**, **f**). In the diabetic patient there is a loss of sudomotor (**b** compared to **a**), pilomotor (**d** compared to **c**) and vasomotor (**f** compared to **e**) nerve fibres. Nerve fibres are in *green* (protein gene product 9.5); basal membranes and vessels are in *red* (collagen IV); epithelia and endothelia are in *blue* (*Ulex europaeus*, agglutinin). Scale bar = 100 μm

despite of the shortness of corneal nerves, CCM is able to detect the length-dependent diabetic SFN even at early stages, and it may represent a reliable noninvasive marker of SFN and a possible surrogate endpoint for nerve fibre regeneration [13].

With regard to *diabetic pain*, loss of IENF itself is neither sufficient nor necessary to result into neuropathic pain and additional/alternative functional factors may play an important role [14]. Spontaneous and paroxysmal pain in the absence of any external stimulus is caused by ectopic impulse generation within the nociceptive pathways due to altered functions of ion channels. Hyperglycaemia and activation of the polyol pathway can induce hyperexcitability through reduced pump activity of NA+/K+ ATPase, altered distribution and functioning of the $K_V1.2$ potassium channel subunit and increased of persistent sodium currents due to upregulation of $Na_V1.7$ and $Na_V1.8$ in nociceptive C-fibres. Upregulation of the transient receptor potential V1 associated with uninjured C-fibres may be also involved causing spontaneous nerve activity induced by normal body temperature [14]. Following the genetic characterization of mutations in the SCN9A ($Na_V1.7$), SCN10A ($Na_V1.8$), SCN11A ($Na_V1.9$) in a wide spectrum of familial painful neuropathies/disorders as well as in idiopathic SFN, it may be hypothesized that several genetic factors may modulate the expression of neuropathic pain in the diabetic population.

18.5.1 Multifocal Neuropathies

In patients with painful proximal neuropathies (LSRP), biopsy of the affected nerves (e.g., the intermediate cutaneous nerve of the thigh) indicated vasculitis of perineurial and endoneurial vessels as the main pathological process.

18.6 Risk Factors and Pathogenesis

DPN results from metabolic dysfunctions, ischaemic factors and inflammation; metabolic dysfunctions prevail in length-dependent DSP/SFN, whereas altered microcirculation and superimposed inflammation prevail in focal neuropathies. The complexity of pathogenesis limits suitable animal models that recapitulate both chronic and/or acute damages leading to DPN [15]. The best model should represent major pathogenetic pathways, should be sensitive to antidiabetics and to antineuropathic drugs and should be suitable for pathogenetic investigations and therapeutical screenings. Better models include the C57BL/Ks (db/db) mice, streptozotocin-induced C57BL6/J and ddY mice, spontaneously diabetic WBN/Kob rats, nonobese diabetic mice, spontaneously induced Ins2 Akita mice and leptin-deficient (ob/ob) mice; high-fat diet-fed female C57BL6/J mice might be suitable models for prediabetic or obesity-related diabetic neuropathy.

Metabolic players include hyperglycaemia, dyslipidaemia and changes in insulin signalling [16].

In either T1DM and T2DM, chronic hyperglycaemia increases oxidative stress by glucose auto-oxidation, production of advanced glycosylation end products

(AGEs) and activation of the polyol pathway, protein kinase C (PKC) and poly (ADP-ribose) polymerase (PARP). Enhanced glycolysis causes an overload of the mitochondrial electron transport chain, generating reactive oxygen species (ROS) which lead to DNA damage and stress of the endoplasmic reticulum (ER). AGEs form through the attachment of reactive carbohydrate groups to proteins, lipids and DNA; AGE peptides bind and activate the cell surface receptor (RAGE) on monocytes and endothelial cells, thus increasing the production of cytokines and adhesion molecules and initiating inflammatory signalling cascades; furthermore, AGE receptor ligation can activate the transcription of the pleiotropic factor NF-κB and contribute to production of various pro-inflammatory mediators. Enhanced flux of the polyol pathways by the excess glucose, which is reduced to sorbitol by aldose reductase (AR) and then to fructose by sorbitol dehydrogenase, causes depletion of the NADPH needed for regeneration of the antioxidant glutathione. Glycolytic intermediates derived from excess glucose, which is shunted into the hexosamine pathway, also contribute to the inflammatory injury. Enhanced activity of PKC isoforms promotes inflammation through the activation of various signalling mechanisms such as mitogen-activated protein kinases (MAPK) and NF-κB.

T2DM-associated dyslipidaemia contributes to the pathogenesis of DPN through various mechanisms: free fatty acids may be toxic to Schwann cells (SC) and promote inflammation; modified (oxidized or glycated) plasma lipoproteins (especially LDL) can bind to extracellular receptors, such as oxidized LDL receptor 1 (LOX1), toll-like-receptor 4 (TLR4) and RAGE, and can activate several signalling cascades leading to oxidative stress.

Since insulin functions as a neurotrophic factor to peripheral neurons, insulin deficiency in T1DM and insulin-resistance in T2DM may concur to the pathogenesis by compromising nerve viability and repair.

All the metabolic alterations described above converge producing complex mitochondrial dysfunction, DNA damage and ER stress, in neurons (axons and nerve terminals), SC and endothelial cells of the nerve microvasculature that, in turn, promote macrophage activation and inflammation [17].

It should be noted that all metabolic pathways and molecular players involved in DPN (Na+ and K+ channels, mitochondria, insulin receptors and insulin-independent glucose transporters which facilitate the diffusion of glucose into neurons and SC) are particularly enriched at Ranvier's node and paranodal region where the greatest cross talk between SC and axons occurs that could contribute to the mixed pattern of axonopathy and schwannopathy [18].

18.7 Diagnosis and Laboratory Investigations

18.7.1 Diabetes and Prediabetes

DM is defined by a 2-h plasma glucose ≥200 mg/dL during an oral glucose tolerance test, fasting glucose ≥126 mg/dL or glycosylated haemoglobin (HbA1c) ≥6.5 %. Prediabetes is a fluctuating and reversible state which identifies patients

who are at an elevated risk for developing DM; it is defined by impaired fasting glucose (fasting plasma glucose between 100 and 125 mg/dL) or IGT (2-h glucose value in an oral glucose tolerance test of 140–199 mg/dL). An HbA1c range of 5.7–6.4 % can also be used to identify prediabetes [19].

18.7.2 DSP and SFN

According to the American Diabetes Association, all patients should be screened clinically for DSP at the diagnosis of T2DM and 5 years after the diagnosis of T1DM and at least annually thereafter [1]. The examination should include ankle reflexes as well as pinprick, temperature and vibration perception (using the 128 Hz graduated Rydel-Seiffer tuning fork) and pressure sensation (using the 10-g Semmes-Weinstein monofilament). Sensations should be assessed at each foot, at the hallux and metatarsal heads 1, 3 and 5. With regard to symptoms, a number of validated questionnaires may help practitioners to diagnose correctly neuropathic pain [20].

There is no uniform consensus regarding the diagnostic criteria. According to Boulton et al. [1], the diagnosis of DPN should include at least two of the following abnormalities: symptoms and/or signs of neuropathy, nerve conduction (NC) changes or altered quantitative sensory testing (QST). According to Tesfaye et al. [21], the diagnosis of DSP can be only "possible" or "probable" when NC changes are lacking. NC and quantitative tests are required for clinical trials or epidemiological studies, but are usually not mandatory in the clinical routine unless the diabetic origin is uncertain, the presentation atypical or a coexisting CIDP suspected.

Conventional neurophysiology may be normal if only small-diameter fibres are damaged. Usually, bilateral and symmetrical abnormalities of NC studies and electromyography (EMG) are first detected in the sensory nerves of feet with decreased amplitudes or absence of the sensory nerve action potentials (SNAP) and, less frequently, of sensory NC velocity (SNCV); subsequently, compound motor action potentials (CMAP) in feet decrease together with mildly prolonged distal motor latencies (DML) and F-waves and with mildly slowed motor NC velocities (MNCV). Initially, needle EMG discloses abnormal spontaneous activity and enlarged polyphasic motor units with decreased recruitment. NC changes in the feet are frequently associated with clinically silent signs of compressive neuropathy of the ulnar and median nerves.

Although several new functional tests have been developed for analysing SFN, their cost-effectiveness and limited standardization should be fully weighed up in the everyday practice [10].

QST is a psychophysical examination of sensory functions which are tested by different thresholds and suprathreshold stimuli (mechanical, pressure, vibration, cold, warm, heat, cold, pain, heat pain) and may be a useful tool in diagnosing SFNs. Besides difficulties in standardizing methods and equipments (there are over 15 devices available commercially), QST needs a full cooperation of patients and

has a relatively poor ability to localize the peripheral or central sites of the somatosensory dysfunction [22]. New nociceptive evoked potentials have mainly a clinical-research role; they include the laser-evoked potentials (LEP) or contact heat-evoked potentials, which activate the Aδ- and C-fibres, and the pain-related evoked potentials (PREP), which activate the Aδ-fibres. Although LEP are independent of patient's attention, they cannot discriminate between the peripheral or central pathways related to pain and temperature.

Skin biopsy is a minimally invasive method that provides a reliable and objective measure of small-fibre involvement [23]. The reduction of IENF is a widely recognized diagnostic criterion of definite SFN in diabetic patients with normal SNCV and length-dependent symptoms/signs of small-fibre damage [21]. Skin biopsy, repeated overtime, allows to study the natural course of the neuropathic process and eventually the regenerative response to therapies. Using this tool, an impaired ability of epidermal axons to regenerate has been demonstrated in diabetic patients after chemical axotomy induced by topical application of capsaicin [24]. Interestingly, an increased IENF density has been found in patients with impaired glucose tolerance [25] and with diabetes [26] after changes of lifestyle and supervised exercise intervention.

CCM is still limited to specialized centres and has mainly a research application.

18.7.3 DAN

Screenings for autonomic dysfunction are based on careful examination and history as well as on testing of cardiovascular reflexes especially in at-risk patients with poor glycaemic control, cardiovascular risk factors and macro-/microangiopathic complications. Testing includes postural blood pressure and measure of heart rate variability (HRV) to deep breathing, standing and Valsalva manoeuvre. Bladder function should be investigated by a urodynamic study in patients with recurrent urinary tract infections or incontinence. Erectile dysfunction not responding to phosphodiesterase-5 inhibitors should be examined to assess the penile, pelvic and spinal nerve function. In sudomotor dysfunction the quantitative sudomotor axon reflex test (QSART) may detect distal SFN with a sensitivity of 75 %.

18.7.4 Asymmetrical Focal/Multifocal Neuropathies

NC studies disclose a multifocal axonal pattern of involvement. In LSRP EMG discloses low femoral-nerve CMAP, prominent fibrillation potentials in thoracic and lumbar paraspinal muscles and active denervation in affected muscles. ESRs and cerebrospinal fluid (CSF) proteins are usually increased. MRI of lumbar spine and lumbosacral plexus may rule out structural radiculoplexopathies and demonstrate signs of inflammation.

18.7.5 Other or Additional Causes of Neuropathy

The diagnosis of DPN involves the exclusion of nondiabetic causes. Investigations should be guided by clinical findings. Coexistence of DPN and CIDP should be investigated by NC studies, MRI of spine, roots and plexuses, nerve ultrasound, CSF analysis and, in selected cases, sural nerve biopsy following the diagnostic guidelines for CIDP [27].

18.8 Therapy

18.8.1 Disease-State Modifiers

Enhanced glucose control is the only disease-modifying therapy for DPN. This statement has a robust evidence in several randomised control trials (RCT) conducted in T1DM with more tight insulin dosing [3, 28, 29], but is weak in T2DM: recent meta-analysis of RCT [30] and a Cochrane review [31] found no significant improvement of T2DM DPN under intensive glycaemic control; nevertheless, besides real differences of T1DM/T2DM trajectories, studies in T2DM were not designed specifically to assess the neuropathy carefully. The effects of pancreas or islet-cell transplantation on DSP in T1DM received limited studies; pancreas transplantation was not accompanied by significant changes in electrophysiology, QST and IEFND (although there was significant corneal regeneration in 15 patients 6 months after the procedure [32]); islet-cell transplantation demonstrated some improvement in neurophysiological end points but not in skin biopsy findings [33].

α-Lipoic acid (ALA) had been found to be well tolerated and capable to provide a clinically meaningful improvement of both positive symptoms and neuropathic deficits when administered at 600 mg/day i.v. [34]; nevertheless, the combination of parenteral (600 mg daily for 3 weeks) and oral therapy (600 mg 3 times daily for 6 months) administered over 7 months [35], as well as a 4-year placebo-controlled, randomized, double-blind trial [36], reported no clinical or neurophysiological improvements; current guidelines by the American Academy of Neurology (AAN) and European Federation of Neurological Sciences (EFNS) do not support the use of ALA [37, 38].

Modifiers of the polyol pathway such as aldose reductase inhibitors (ARI) have been investigated thoroughly; only epalrestat is commercially available in India and Japan. A Cochrane meta-analysis which included 32 trials found no overall significant difference between the treated and control groups although one subgroup (4 trials with tolrestat) favoured treatment; furthermore, three ARIs had dose-limiting adverse effects that caused withdrawal of their use in humans: liver toxicity with tolrestat, elevation of creatinine with zenarestat and severe hypersensitivity with sorbinil [39].

Other modifier options are under investigation including angiotensin-converting enzyme (ACE) inhibitors, protein kinase C β-inhibitor, medical foods such as folate and B vitamins, insulin C-peptide and lipid-lowering diets or drugs (statins, fenofibrate) [9].

18.8.2 Symptomatic Treatment of Pain

Pain management is essential for improving the quality of life of DPN patients. Several consensus guidelines are available providing the best-evidence practice [37, 38]. Although algorithms may differ in choosing the first-line and the second-line agents, most guidelines include tricyclic agents (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and epileptic drugs (AED) within first-line options and opioids within second-line options. The choice of the first drug depends mainly on the side-effect profile related to comorbidities of each patient; the preferred drug should be titrated to the maximum tolerated dose before switching to another first-line drug, to a combination therapy or to a second-line agent; most agents require a 4–6-week trial to assess efficacy.

Acetaminophen (paracetamol) does not attenuate neuropathic pain but may be helpful if neuropathic pain is exacerbated by nociception. Nonsteroidal anti-inflammatory drugs (NSAIDs) are often prescribed for short-term analgesia; however, due to potential harmful side effects (e.g. haemorrhage, exacerbation of renal dysfunction), their use has not been studied extensively so that they are not included in common guidelines.

TCA antidepressant (amitriptyline, imipramine, desimipramine) were the first medications with proved effect on neuropathic pain in placebo-controlled trials. They have multimodal actions including blocking of serotonin and noradrenaline reuptake, as well as blocking of histaminic, cholinergic and α1-adrenergic receptors and of sodium channels [9]. The heterogeneity of sites of actions explains their multiple side effects (orthostatic hypotension, slow cardiac conduction, cardiac arrhythmias, increased heart rate, drowsiness, weight gain, constipation, dizziness, blurred vision, urinary retention and precipitation of narrow-angle glaucoma). Although side effects may limit the use of TCA, they may be partially overcome by slow titration: the starting dose for amitriptyline is 10–25 mg at night that may be increased by 10–25 mg at night every 3–7 days up to 75 mg.

Serotonin-norepinephrine reuptake inhibitors (SNRI) are also supported by major guidelines [37, 39]. Recommended doses are 60–120 mg daily for duloxetine and 75–225 mg daily for venlafaxine; common minor sides effects include nausea, somnolence and constipation observed usually with higher dosages and can be limited by slow titration starting (e.g. starting dose for duloxetine = 30 mg/day).

The AED gabapentin and the higher potent gabapentoid pregabalin bind to the α2-δ subunit of calcium channels and inhibit the release of neurotransmitters. Recommended daily doses are 300–600 mg (divided into two doses) for pregabalin and 900–3600 mg (divided into three doses) for gabapentin. Common side effects include somnolence and dizziness; cerebral oedema due to abrupt discontinuation and ankle oedema have been also reported with pregabalin [9]. Among AED, lamotrigine, carbamazepine and oxcarbazepine are not recommended [37, 39].

Opioids are recommended as second-line agents if all the three classes of first-line drugs or their combinations have failed. The use of opioids should be carefully considered taking into account side effects (dose-related respiratory depression,

confusion, delirium, bradycardia/tachycardia, orthostatic hypotension, urinary retention, constipation), the long-term adverse effects of dependency and abuse, changes in immunological functioning, suppression of the pituitary axis and risk of aberrant opioid use [9]; such a risk should be evaluated through the use of a validate screening methods such as the Opioid Risk Tool or the Diagnosis, Intractability, Risk, Efficacy score [40]. EFNS recommended controlled-release oxycodone (daily dose 10–60 mg daily) and tramadol (200–400 mg a day or tramadol 37.5 mg with 325 mg acetaminophen) [38]; AAN recommended controlled-release oxycodone (mean 37,5 mg a day, up to 120 mg a day), morphine (up to 120 mg a day) and tramadol (210 mg a day) [37]. Among new opioid analgesic available to treat severe chronic pain, tapentadol extended release (ER) controls both nociceptive and neuropathic pain by acting through an opioid spinal-supraspinal synergy, as well as through an intrinsic spinally mediated μ-opioid receptor agonist-norepinephrine reuptake inhibitor effect (MOR-INR) [41]. The starting dose is 50 mg twice daily which may be slowly titrated up to 500 mg a day; side effects include commonly headache, drowsiness, dizziness, nausea, constipation and, uncommonly, syncopes and instability.

Topical treatments with capsaicin cream and lidocaine 5 % patches may be useful in decreasing focal pain and were included within potential therapeutic options by the AAN guidelines [37]. Botulinum toxin type A, which may provide a relief of neuropathic pain through a modulation on afferent sensory fibre firing, is considered probably effective by EFNS [38] but it is not included by AAN [37].

Among non-pharmacological approaches in managing pain of diabetic neuropathy, transcutaneous electric nerve stimulation can also be considered [42]. There are no sufficient evidences supporting or disclaiming the use of acupuncture in DPN [43].

18.8.3 Treatment of DAN

There is no treatment that can effectively stop or reverse clinically evident DAN. Apart from a preventive role of intensive glycaemic control in T1DM, of multifactorial cardiovascular risk reduction and of lifestyle intervention, definite recommendations cannot be given [44]. Symptomatic orthostatic hypotension may be treated by physical countermanoeuvres and by therapy with the α1-adrenergic agonist midodrine and/or mineralocorticoid fludrocortisone. Symptomatic gastroparesis may be approached with low-fat/fibre diets and prokinetic drugs. Treatment of diarrhoea and constipation is symptomatic; bacterial overgrowth may occur in up to 40 % of diabetic patients and should be treated with antibiotics.

18.8.4 Treatment of LSRP

Although some case reports suggest that patients with LSRP may benefit from intravenous methylprednisolone or immunoglobulins in controlling pain and positive

neuropathic symptoms, there is no evidence from any trial supporting the use of immunotherapies [45].

Key Points

- Diabetic neuropathies encompass the whole spectrum of peripheral neuropathies and may develop at any time along the natural history of T1DM or T2DM.
- Distal symmetrical polyneuropathy (DSP) is the most common clinical form; all diabetic patients should be screened for DSP at the time of diagnosis and annually thereafter.
- Painful small-fibre neuropathy (SFN) is increasingly recognized as an early manifestation of DSP. SFN may have no abnormalities on nerve conduction studies and they may be confirmed by skin biopsy, which measures the intraepidermal nerve fibre density, and by sudomotor testing.
- SFN is increasingly recognized in individuals with prediabetes. An oral glucose tolerance test and/or a measurement of HbA1c values should be performed in a patient with otherwise idiopathic neuropathies.
- Cardiac autonomic neuropathy is usually associated with SFN and may lead to life-threatening complications.
- Enhanced glucose control is the only disease-modifying therapy for DSP.
- Neuropathic pain is the most common complication of diabetic neuropathy. First-line agents for the treatment of pain include amitriptyline, venlafaxine or duloxetine, gabapentin or pregabalin or a combination of them. The choice of the first drug depends on the side-effect profiles and comorbidities of each patient.

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Infectious Neuropathies

19

Sergio Ferrari, Sara Mariotto, Tiziana Cavallaro, Gianmaria Fabrizi, and Salvatore Monaco

19.1 Introduction

Infectious agents are common causes of *neuropathy* in endemic areas, while they are rarely observed in other regions. However, in the current era characterized by quick and easy migration processes, the knowledge of the main infectious neuropathies is required. In the course of infectious diseases, the peripheral nervous system (PNS) may be affected by direct infiltration of peripheral nerves, indirect damage induced by immune and inflammatory responses, or therapy-induced toxicity.

19.2 Hepatitis C Virus (HCV)-Related Neuropathies

PNS is frequently affected in the course of *HCV infection*. Peripheral nerve involvement can be due to a direct viral damage, the presence of *cryoglobulinemia* (CG), and the multiple comorbidities that affect HCV-infected patients. CG is the most frequent extrahepatic manifestation of HCV infection, detectable in up to 50 % of patients, and is the most important risk factor for the peripheral nerve involvement. Cryoglobulins (CGs) are cold-precipitable immunoglobulins, which deposit in small- and medium-sized vessels and cause ischemic damages, lymphocytic microvasculitis, and/or necrotizing arteritis, with polymorphonuclear cell infiltration. Three types of CG are recognized: type I consists of monoclonal immunoglobulin (Ig), and type II is a mixture of monoclonal and polyclonal Ig, while type III is composed of polyclonal Ig. "Mixed cryoglobulinemia" (MC) is defined by either type II or III CG and in up to 95 % of cases is associated with chronic HCV/HIV

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infection. About 17–60 % of patients with CG develop peripheral neuropathy (PN), often at disease onset [1, 2]. Neuropathy is rarely seen in patients with HCV infection and type I CG. In our experience axonal polyneuropathy is the main presented form, pathologically characterized by perivascular infiltrates, endoneurial purpura, and microangiopathy, overall suggesting an ischemic pathogenesis linked to endoneurial microcirculation obstruction [3]. Conversely, in patients with HCV-associated MC, the PNS involvement is frequently observed and is more severe when a higher cryocrit is present. *Pathological features* are consistent with axonal degeneration, loss of myelinated fibers (Fig. 19.1) and small-vessel vasculitis or necrotizing arteritis of medium-sized vessel with consequent ischemic nerve damage [4]. In the less frequently reported cases of HCV-associated neuropathy without CG, the vascular and perivascular inflammation can be due to a direct HCV damage or HCV-induced autoimmune mechanisms. Actually, HCV active replication has never been demonstrated in the PNS, and the observation of HCV-RNA in epineurial cells, in close relationship with mononuclear inflammation, is in favor of an immune-mediated pathogenesis [5, 6]. According to previously reported studies, the most frequent form of neuropathy observed in HCV-infected patients is a length-dependent symmetric sensory or sensorimotor axonal polyneuropathy, clinically characterized by distal sensory loss and weakness. More recent reports describe sensory neuropathy as the most prevalent neuropathic form of HCV infection [7].

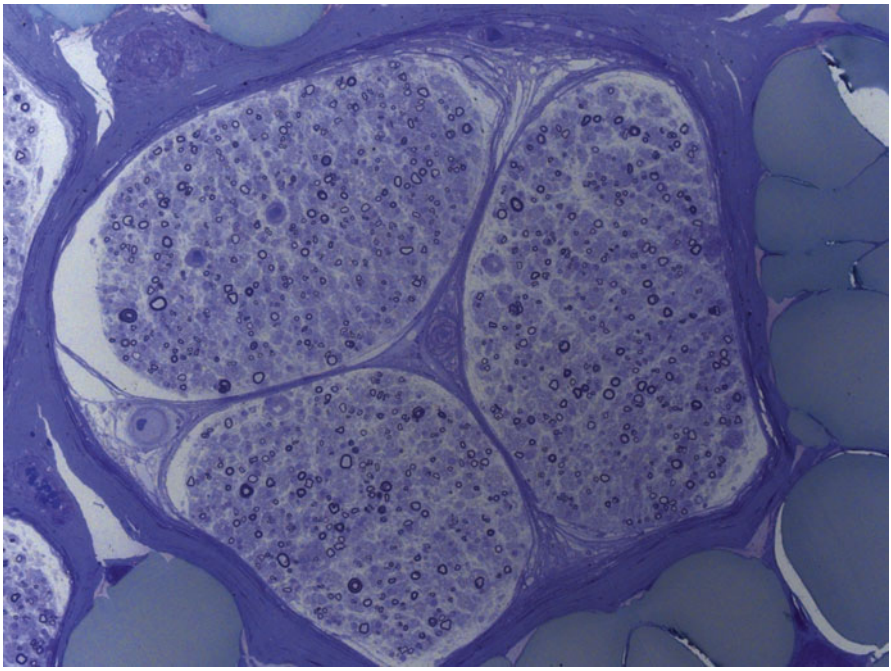

Fig. 19.1 Sural nerve fascicles showing asymmetric loss of myelinated fibers in a patient with cryoglobulinemic neuropathy and HCV infection (toluidine blue, original magnification ×50)

Sensory neuropathy can be distinguished in symmetric or asymmetric forms, the latter variants including *large-fiber sensory neuropathy* (LFSN) and *small-fiber sensory neuropathy* (SFSN). LFSN usually manifests with sensory loss, paresthesias, numbness, and cramps, while SFSN is characterized by burning feet, tingling, restless leg syndrome, and sometimes a non-length-dependent pattern suggestive of ganglionopathy [8]. In some cases the damage of both small and large fibers may coexist. *Mononeuropathies* and *mononeuropathy multiplex* (MM), characterized by stocking-glove asymmetric neuropathy or overlapping forms have also been reported. In a prospective clinical, neurophysiological, and skin biopsy study recently reported, Biasiotta and colleagues described 47 subjects with PN and 29 with neuropathic pain in a series of 69 patients with HCV-related CG. The authors describe a prevalence of predominantly sensory distal polyneuropathy and report the relevance of nociceptive pathway damages. They also note an association between neuropathy, age, and HCV infection rather than CG [9]. Unusual forms of HCV-associated neuropathy are those of pure *motor polyneuropathies* [10] and *autonomic neuropathies* [11]. Cranial nerve damages have been anecdotally described as an involvement of the abducens, facial, and motor trigeminal nerves. Intriguingly, the spectrum of PN in the course of HCV infection is not limited to axonal forms, but encompasses a number of demyelinating conditions. The association between *Guillain-Barré syndrome* (GBS) and non-A, non-B hepatitis has been described before the discovery of HCV [12] and, more recently, in patients with chronic HCV infection [13]. Acute inflammatory demyelinating polyneuropathy (AIDP), the demyelinating variant of GBS, has been described in a single case with subclinical HCV infection during the pre-convalescent phase [14]. As for chronic forms of neuropathy, few reports describe an association between HCV infection and *chronic inflammatory demyelinating polyneuropathy* (CIDP) [15]. This form can be also seen as an uncommon side effect in patients treated with *IFNα* which could have immunomodulating effects as a reduction of proinflammatory cytokines and, at the same time, could play a major role in triggering immune-mediated mechanisms [16]. A single case of Lewis-Sumner syndrome, an asymmetric form of CIDP, has been described in the course of HCV infection; these patients improved after high-dose intravenous immunoglobulins (IVIG) and methylprednisolone treatment, relapsed after administration of INFα and ribavirin, and finally recovered after the discontinuation of INF coupled with e.v. methylprednisolone [17]. We recently reported an intriguing association between HCV infection and neuropathy with *anti-MAG* (myelin-associated glycoprotein) antibodies, which is usually reported in association with hematological disorders or, more rarely, with primary amyloidosis, cryoglobulinemic vasculitis, Charcot-Marie-Tooth type 1, or amyotrophic lateral sclerosis and HCV infection [18]. This neuropathy is usually characterized by a distal demyelinating disorder that involves large fibers and manifests as sensory ataxia, mild motor involvement, and hand intention tremor. Significant weakness and small-fiber neuropathy are encountered in few atypical cases. We studied a cohort of 59 consecutive patients with neuropathy and chronic HCV infection who had undergone nerve biopsy. We detected CG in 39 patients (18 cases with axonal polyneuropathy, 11 with overlapping MM, and 10 with MM). In 14 patients,

CG has not been detected, but they resulted positive for rheumatoid factor (RF); 10 of them had an axonal polyneuropathy, 1 an overlapping form, and 3 cases an MM. Surprisingly, in 3 of the 6 patients without CG or RF, IgM monoclonal gammopathy with anti-MAG activity was detected. Nerve biopsy showed loss of fiber and ongoing segmental demyelination with onion bulb formation, mild perivascular infiltrates of lymphocytes and monocytes at the epineurial level in one case, and endoneurial edema and microangiopathy in the other one. IgM and complement deposition has been observed on myelin sheaths in all three cases. The high association between anti-MAG neuropathy and HCV infection could be the result of the production of monoclonal and polyclonal immunoglobulins triggered by HCV-induced B-cell expansion. These data are supported by the recent description of a significant association between anti-GM1 gangliosides and anti-sulfatide antibodies and HCV-related PN. As for the treatment of HCV-related neuropathy, *antiviral therapy* is the first therapeutic choice, but studies with rituximab have also been performed. According to a recent Cochrane review, high-quality studies are lacking, and there are insufficient data to make an evidence-based decision [19].

19.3 Human Immunodeficiency Virus (HIV)-Related Neuropathies

PN is considered the most common neurological complication of *HIV infection*, even after the introduction of *combination antiretroviral therapy* (cART). The increase in life expectancy is linked to a prolonged exposure to neurotoxic antiretroviral therapies and their potential complications. Various types of PN have been reported in association with HIV infection, including distal symmetric polyneuropathy, *toxic neuropathy* induced by antiretroviral drugs, demyelinating neuropathies, mononeuropathy multiplex, diffuse infiltrative lymphocytosis syndrome (DILS), and progressive polyradiculopathy [20]. The diagnosis and appropriate treatment of PN in the course of HIV infection represent a challenge also for expert neurologist and for consultant in infectious diseases. The difficulty lies in the overlap between the different forms of PN and the frequently unusual clinical presentations.

19.3.1 Distal Symmetric Polyneuropathy (DSP)

DSP is the most common form of neuropathy in the course of HIV infection. Its prevalence in cART era ranges from 20 to 60 % [21]. According to some studies, the most important risk factors for DSP are age, height, and stavudine exposure, while it seems not associated with decreased *CD4* count or increased viral load [22]. On the contrary, other studies identify the lower CD4 nadir reached during HIV infection as the leading risk factor for DSP [23]. The clinical presentation of DSP is characterized by a distal symmetric predominantly *sensory neuropathy* with painful feet and hyperpathia. Neurological examination reveals decreased or absent ankle

tendon reflexes with impaired pinprick and vibration sensations. Distal muscle weakness is usually mild or absent. According to recent studies, *autonomic dysfunction* including orthostatic hypotension, gastroparesis, diarrhea, constipation, urinary incontinence, sexual dysfunction, sweating, and pupillary abnormalities is commonly associated with DSP in HIV subjects [24]. Electrophysiological studies may be useful to confirm a length-dependent axonal polyneuropathy with small or absent sural sensory nerve action potentials. It also allows to distinguish between DSP and PNS demyelinating conditions as CIDP. Total Neuropathy Score (TNS) [25] and Brief Peripheral Neuropathy Screen (BPNS) [22] are the main clinical tools used to assess DSP. TNS has been validated in diabetic neuropathy and analyzes both the grading of sensory, motor, and autonomic symptoms and signs and nerve conduction studies. BPNS is a quick and easy clinical score that includes questions about neuropathic symptoms, examination of vibration at the great toe, and ankle reflexes. The *neuropathological features* of DSP at sural nerve biopsy are usually characterized by loss of myelinated and unmyelinated fibers with variable extent of axonal degeneration and macrophage infiltration. Demyelinating features are more rarely observed and are considered secondary to axonal damage. The direct detection of HIV in nerve fascicles has been rarely observed indicating the variable nature of this form [26]. Autoptic series show that fiber loss and axonal degeneration prevail in the distal regions of peripheral nerves rather than in the proximal ones, confirming the length-dependent nature of this polyneuropathy. Distal *skin biopsies* may show a loss of the epidermal nerve fiber that correlates with neuropathic pain scores [27]. The differential diagnosis of DSP always requires the exclusion of other causes of neuropathy such as alcoholism, diabetes mellitus, vitamin B12 deficiency, monoclonal gammopathy, and uremia. Moreover, in the course of *antiretroviral therapy*, the patient may present with a clinical picture similar to DSP. Finally, the introduction of *cART* can induce per se DSP through the toxicity due to antiretroviral reverse transcriptase inhibitors as didanosine, zalcitabine, and stavudine. DSP associated with antiretroviral therapy has usually a faster onset and a more rapid course compared to HIV-DSP. Actually, the exact cause of axonal damage of small myelinated and unmyelinated nerve fibers in patients with HIV-DSP has not been established. A direct neuronal damage induced by HIV infection is unlikely since neurons do not express CD4 receptor that is required for the entry of the virus into the cells. Soluble HIV viral gene products as gp120 and viral protein R (*Vpr*) were used in experimental models in order to assay neurotoxicity. Gp120 is a coat glycoprotein that mediates the binding and transmission of HIV into cells by interaction with CD4 receptor via C-C chemokine receptor type 5 (CCR5). Vpr is a protein with cytotoxic effects that modulates HIV infectivity and increases oxidative stress. Recent in vitro studies suggest a primary role of *macrophage activation* in the induction of sensory neuron damage due to an indirect action of HIV protein gp120 that stimulates macrophages by CCR5 binding. These data are confirmed by the inhibitory effect of gp120-induced tumor necrosis factor gene expression, obtained with maraviroc, a CCR5 antagonist [28]. Since pain is the major symptom in patients with HIV-DSP, pain management is the main target of current treatment. Off-label *treatments* include the use of different classes of drugs: nonsteroidal inflammatory drugs, topical agents

(lidocaine and capsaicin), tricyclic antidepressants (amitriptyline, duloxetine), anticonvulsant agents (gabapentin, pregabalin, lamotrigine), and opioids (oxycodone, morphine, and fentanyl patch). In clinical practice a combination of different drugs with distinct specific mechanisms of action is frequently needed to achieve relief from neuropathic pain. A recent meta-analysis of seven randomized double-blind studies demonstrated the efficacy of high-dose (8 %) *capsaicin patch* in single application: 41 % of patients with HIV-DSP obtained 30 % relief of neuropathic pain, and 7 % had complete analgesia starting within few days after treatment and lasting after an average of 5 months [29]. *Pregabalin* resulted to be effective in a small placebo-controlled trial but failed to show relief of pain according to a randomized double-blind placebo-controlled trial [30]. As shown in a placebo-controlled trial performed by Abrams and colleagues, smoked *cannabis* produced a significant reduction of pain in DSP [31]. Among the disease-modifying drugs, human recombinant nerve growth factor (hrNGF) seems to be more effective than placebo; however in a more recent open-label study, hrNGF did not cause an improvement in the severity of neuropathy [32]. Given the lack of concordance of the different studies, this drug has been withdrawn in patients with HIV-associated neuropathy. According to literature, other disease-modifying drugs, as acetyl-L-carnitine, prosaptide, and peptide T, did not show significant efficacy in DSP.

19.3.2 Demyelinating Neuropathy

Demyelinating neuropathies as *AIDP* and *CIDP* have been reported in acute and chronic forms of HIV infection. Due to the lack of large series and controlled studies, the incidence of AIDP and CIDP in the course of HIV infection is unknown. AIDP frequently occurs in the early stage of HIV infection, sometimes preceding the diagnosis of AIDS, when the immunosuppression is less pronounced. Even if CIDP may occur in early HIV infection, it frequently manifests in more advanced stages of the disease. Cases of *Miller Fisher syndrome* associated with HIV seroconversion and a patient who developed Miller Fisher/AIDP overlap in the presence of serum anti-GQ1b antibodies have been also reported [33]. In these patients, clinical features, disease course, and neurophysiological findings appear similar to that of HIV-negative patients. In accordance, in AIDP cases the nadir of neurological signs is reached within 4 weeks, whereas in CIDP the neurological impairment progresses for more than 8 weeks and may be relapsing and remitting.

Neurophysiological analysis shows slow conduction velocities, increased distal motor and F-wave latencies, and partial conduction blocks, characteristics of demyelinating neuropathies. At *cerebrospinal fluid* (CSF) examination, high protein content is frequently observed, but, at variance with non-HIV inflammatory polyneuropathies, a mild lymphocytic pleocytosis is frequently found. Brannagan et al. reviewed ten cases with HIV-AIDP and observed a CSF with blood cell count of less than 10/mm^3 in seven cases, concluding that the absence of pleocytosis in AIDP patients does not exclude HIV infection [34]. Like in non-HIV patients, *pathological examination* of the peripheral nerve in CIDP cases shows demyelination and

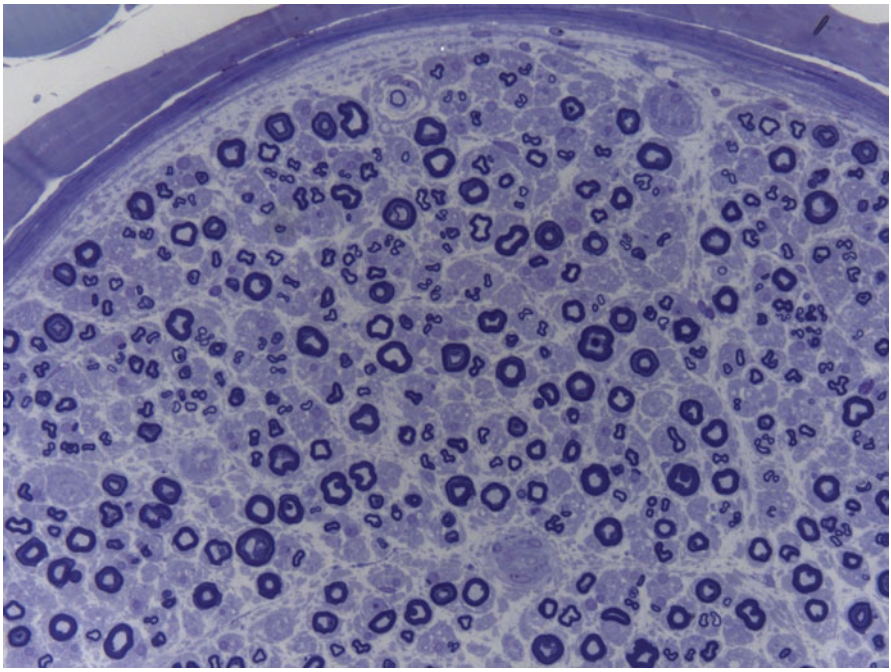

Fig. 19.2 Sural nerve biopsy in a patient with HIV-associated CIDP. Some onion bulb formations are evident at toluidine blue stain (original magnification ×100)

onion bulb formation (Fig. 19.2), infiltration of mononuclear cell of nerve fascicles, and endoneurial edema. *Treatment* of AIDP includes IVIG and *plasmapheresis*. Clinical signs of CIDP may improve with *steroids*, IVIG, or plasmapheresis, but IVIG are considered the treatment with fewer complications. Finally, some data suggest that patients with clinical picture of AIDP and CD4 count less than 50 cell/μL should be treated presumptively for *cytomegalovirus (CMV)* infection, but some cases reported by Brannagan et al. do not support this recommendation [34].

19.3.3 Mononeuropathy Multiplex (MM)

MM, characterized by asymmetric sensorimotor involvement of single nerves, is a rare complication occurring in early and late stages of HIV infection. The initial asymmetric involvement of peripheral nerves may progress, during the evolution of the disease, in a clinical picture simulating a distal symmetric neuropathy. If occurring at the onset of HIV infection, MM is the result of self-limited immune-mediated *vasculitis*. Vasculitis is a rare event in HIV infection and occurs only in 0.3–1.0 % of patients with AIDS either as an isolated process involving peripheral nerves or as a manifestation of a systemic disease. In post-cART era, vasculitis of PNS may present as distal symmetric polyneuropathy [35]. The *pathological features* of nerve

biopsy show focal loss of fibers, variable axonal degenerations, and perivascular epineurial inflammatory cell infiltration with fibrinoid necrosis. In the later stages of the infection, when fewer than 50 CD4 cells/μL are present, MM can be associated with *CMV* infection or, more rarely, with *varicella zoster*, *HCV*, or *lymphomatous infiltration* of nerve. CMV is an opportunistic agent that affects HIV-infected patients with fewer than 50 CD4 cells/μL. Clinical picture of CMV infection includes a multiorgan involvement with retinitis, pneumonia, gastrointestinal system involvement, epididymitis, pancreatitis, cervicitis, hepatitis, encephalitis, and MM or polyradiculopathy. Nerve biopsy shows lymphomonocyte cell infiltration of nerve fascicles and the presence of cytomegalic cells filled with CMV particles.

19.3.4 Progressive Lumbosacral Polyradiculopathy (PLP)

Progressive lumbosacral polyradiculopathy (PLP) starting with back and leg pain and evolving into paraparesis with sensory and sphincter dysfunction has been frequently observed in HIV-infected subjects pre-cART era [36]. PLP usually occurs in the late stages of HIV infection in concomitance with low count of CD4 lymphocytes. Usually PLP is related to *CMV* infection, but it can be caused by different conditions including mycobacterial, syphilis, cryptococcus, herpes simplex infection, and lymphomatous infiltration [20]. The diagnosis includes *CSF* examination with polymerase chain reaction amplification to detect viral agents, mycobacterial and cryptococcus antigen testing. In our experience cytofluorimetric analysis of CSF is helpful and should be recommended in the suspect of lymphomatous meningoradiculitis. *Electrophysiological study* shows denervation in paraspinal muscles followed by denervation potential in the legs in the course of disease progression. Contrast-enhanced MRI can reveal enhancement of nerve roots [37]. *Treatment* for CMV infection should be started early in clinical suspicion of PLP and include ganciclovir, valganciclovir, foscarnet, cidofovir, and fomivirsen.

19.3.5 Diffuse Infiltrative Lymphocytosis Syndrome (DILS)

Diffuse infiltrative lymphocytosis syndrome (*DILS*) is a rare multisystem syndrome described in HIV-infected patients and characterized by persistent blood polyclonal CD8 T-cell lymphocytosis and organ infiltration [38]. This syndrome may affect the salivary glands, lymph nodes, lungs, liver, kidneys, digestive tract, and PNS. *Polyneuropathy*, *aseptic meningitis*, and *facial nerve palsy* are the neurological abnormalities most frequently reported. DILS neuropathy usually presents as a painful and symmetric neuropathy. Electrophysiological examination shows signs of axonal neuropathy. Nerve biopsy is characterized by angiocentric CD8 T-cell infiltration without vessel wall necrosis and abundant expression of HIV p24 protein in macrophages [39]. In these patients, chronic HCV infection and *immune reconstitution inflammatory syndrome* (*IRIS*) are the principal differential diagnosis

to be considered. *Treatment* of DILS consists mainly of *cART*, but *steroids* may also be added when organ infiltration persists.

19.3.6 IRIS and Peripheral Nervous System

IRIS is an aberrant immune response due to the restoration of the immune system that occurs in the cART era. IRIS is defined as an unmasking or paradoxical worsening of a pre-existing infection in the presence of rapid decrease of viral load and recovery of *T-cell* immunity. In the course of IRIS, peripheral nerve involvement can occur in subjects previously affected by *Mycobacterium leprae* infection, inflammatory demyelinating radiculopathy, and cryptococcal radiculoplexopathy. IRIS-associated *AIDP* has also been described. *Treatment* is controversial and includes the use of *anti-inflammatory*, *corticosteroids*, *IVIG*, and *plasmapheresis*.

19.4 Leprosy

Mycobacterium leprae (*ML*) is an obligatory intracellular agent with tropism for macrophages and Schwann cell, which infects the skin and peripheral nerves resulting in chronic inflammation and neuropathy. The prevalence of leprosy is declining but, according to WHO data, it remains a common cause of neuropathy in 17 highly endemic countries. About 81 % of all new cases occur in three countries: Brazil, India, and Indonesia [40]; however, it is a worldwide problem since new cases have also been reported in travelers from endemic areas. Transmission of ML occurs via nasal mucosa and is followed by hematogenous spread. According to the classification of Ridley and Jopling, leprosy is subdivided into different subtypes: tuberculoid (T), borderline tuberculoid (BT), borderline (B), borderline lepromatous (BL), and lepromatous (L). A further form was later defined as indeterminate (I) [41]. The classification is based on the balance between bacterial particles and *immune reaction*. Patients with L form are anergic to the bacillus and examined tissues are rich in mycobacteria. On the other hand, in T form a strong immune reaction with paucity of mycobacteria particles is usually observed. In these latter cases, the immune response is able to limit bacterial growth, but skin lesions and nerve damage are frequently observed. Clinical condition correlates with the entity of activation of cell-mediated immune response to ML. To simplify, the WHO recommended a dichotomic classification into *paucibacillary* (PB) and *multibacillary* (MB) category. PB group includes I, T, BT, B, and BL forms, whereas MB includes BT, B, BL, and L subtypes. The two classifications are considered complementary, but the Ridley and Jopling one fits better with patients' clinical condition and prognosis. The suspect of ML infection is established when *multifocal neuropathy* is associated with hypopigmented, hypoesthetic, or reddish *skin lesions*, even if some patients may present signs of neuropathy in the absence of the characteristic skin lesions. Indeed, 3–10 % of patients present the *pure neuritic form* (PNL) that manifests as PN without any skin lesion. At onset *sensory symptoms* are the most common ones; small fibers

are affected early, whereas large fibers are involved later. Clinical characteristics of PN in the course of leprosy include mononeuritis, MM, and polyneuropathy. *Mononeuritis* is the most common presentation and usually affects nerves of the upper limbs as ulnar, median, posterior auricular, and superficial radial. Lower limbs can also be affected with the involvement of common peroneal, superficial peroneal, and posterior tibial. Rarely, also cranial nerves, primarily facial and trigeminal ones, are damaged [42]. Typically, in the course of ML infection nerves are enlarged and painful on palpation, and electrophysiological examination shows axonal damage. The use of imaging techniques as *nerve sonography* and MRI may be useful in the diagnosis. Analyzing high-resolution sonography, Visser and colleagues showed that the epineurium of the ulnar nerve is often strikingly thickened in these patients, especially in those with ulnar involvement [43]. Symmetric *polyneuropathy* is rarely reported in leprosy, while regional *autonomic* dysfunctions are frequently observed. Although the diagnosis of leprosy is mainly clinical, peripheral *nerve biopsy* can be helpful especially in atypical cases or in those patients with pure neuritic forms. The definite diagnosis is based on skin smear or biopsy demonstrating granulomatous inflammation or foamy macrophages with acid-fast bacilli (Fig. 19.3).

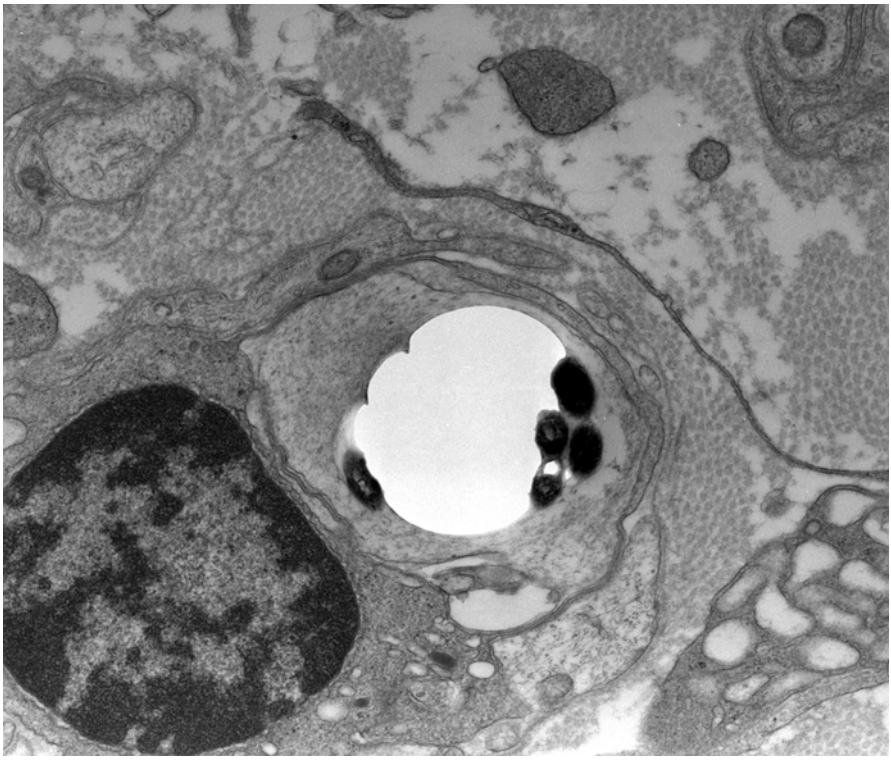

Fig. 19.3 Electron micrograph of sural nerve biopsy in pure neuritic form of leprosy showing a Schwann cell containing *Mycobacterium leprae* organisms (original magnification ×12,000)

19.5 *Borrelia burgdorferi*-Related Neuropathies

The tick-borne spirochete *Borrelia burgdorferi* is responsible of a vector-borne disease, known as Lyme borreliosis, transmitted by the *Ixodes* complex. This *zoonosis*, more diffuse in temperate regions and rural areas, causes a multisystem disease that affects humans as incidental hosts. The skin and the nervous system are the main involved organs. Nervous system involvement can occur through the hematogenous or transneural spread along peripheral nerves, few weeks after a tick bite or in the late and chronic disease [44]. Subacute painful *meningoradiculitis*, which consists of painful migrant burning radiculitis, peripheral motor deficit, and *CSF* inflammation, alone or in combination, is the prevalent manifestation of early neuroborreliosis. Motor damage consists frequently of bilateral and asymmetric peripheral facial nerve palsy. More rarely, III or VI cranial nerve involvement is present, sometimes only observed at MRI [45]. Isolated or concomitant limb paresis often bilateral, asymmetric, and predominantly proximal can occur. These symptoms are consistent with root or plexus lesions and, more rarely, with a distal *mononeuropathy.* Distal *nerve pathology* has been demonstrated in the course of Lyme borreliosis and confirmed by sural nerve findings of small lymphocytic infiltration around endoneurial vessels, perineural fibrosis, and wallerian degeneration [46]. However, nerve involvement in the absence of radicular symptoms or CSF inflammation has been rarely described [44]. *Brachial neuritis*, *Guillain-Barré*, and *CIDP*-like syndrome have also been reported [47, 48]. On the other hand, patients with chronic dermatoborreliosis can develop a distal mainly *sensory neuropathy* in the absence of CSF inflammation. It consists of a mild distal axonal neuropathy probably due to a cutaneous neuritis. Sural *nerve biopsy* show lymphocytic perivasculitis and wallerian degeneration. On the basis of these data, the opportunity to perform the screening for *Borrelia* in patients with PN of unknown etiology, in the absence of the above described symptoms, is still very controversial. Since there is a high percentage of positive *anti-Borrelia IgG* blood test in the general population, the association between polyneuropathy and this infectious agent must be demonstrated by the concomitance of specific markers of active *Lyme borreliosis* as *CFS* pleocytosis, increased protein concentration, intrathecal IgM and IgG synthesis, and PCR positivity in CSF or blood. The data previously reported are mainly referred to European experience, since in American studies the involvement of peripheral nerve has been rarely reported. In early neuroborreliosis, radiculopathy, cranial neuropathy, and MM have been described, while late symptoms as a distal polyneuropathy with mild diffuse stocking-glove process are rarely reported [44]. *Biopsy of sural nerve* shows a prevalent axonal damage with perivascular infiltration [49, 50]. The acute neurological involvement in the course of borreliosis has usually a benign course, but *antibiotics* as penicillin, cephalosporin, ceftriaxone, or oral doxycycline accelerate clinical recovery and prevent the development of new neurological deficit. Also chronic symptoms frequently ameliorate with antibiotic *treatment.* Of note, some patients report long-lasting and relapsing, recurrent, and persistent nonspecific symptoms with negative active *Borrelia* serology. Patients do not improve after antibiotic treatment leading to the idea that the pathogenesis of this condition, known as

"chronic arthropod-borne neuropathy," could be linked to toxins and immunological, autoimmune, or psychological illness rather than the infectious agent [44].

Key Points

- Neuropathy remains the most common neurological complication of HIV infection.
- Different forms of neuropathy may occur during HCV chronic infection, frequently associated with cryoglobulinemia.
- Lepromatous neuropathy may present in pure neuritic form, requiring diagnostic nerve biopsy.
- The association of neuropathy with anti-*Borrelia* IgG antibodies in serum must be confirmed with blood and CSF demonstration of infectious activity.

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Toxic Neuropathies

20

Guido Cavaletti and Paola Marmiroli

20.1 Introduction

The high metabolic rate and the limited capacity of the nervous system to recover from damage explain why toxic injury may be particularly frequent and clinically relevant in different settings. The peripheral nervous system (PNS), despite repair is more effective, is more vulnerable than the central nervous system to toxic insults because the blood-nerve barrier is by far less stringent than the blood-brain barrier. Moreover, virtually no effective barrier exists at the dorsal root ganglia (DRG) level. As a result, several toxic agents can reach the peripheral nerves and, even more easily, the DRG neurons.

This specific vulnerability of the DRG contributes to explain why most of the clinical features of toxic neuropathies are represented by sensory disturbances, although clinically relevant motor and autonomic impairment can also be present in some case.

Several compounds have been reported to be toxic on the PNS, but scientific and epidemiological data indicate that causal relationship is clearly established only for some of them. In fact, temporal relationship between the exposure to a given compound and the onset of PNS impairment is frequently the only evidence supporting causality. Criteria have therefore been proposed to strengthen the validity of this association, including (1) evident dose relationship, (2) proximity of symptoms to compound exposure, (3) stabilization or improvement after withdrawal from substance exposure, (4) possibility to reproduce the clinical features in animal models, and (5) similar clinical features in different subjects [1]. However, these criteria can be unable to capture a real relationship in specific instances, such as prolonged

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exposure to very low doses of toxic compounds that need to reach a threshold in order to determine PNS injury, or when worsening occurs after exposure withdrawal (the "coasting" effect), and improvement is prevented by severe axonal damage. Moreover, animal models of PNS damage [2–4] have never been reported for agents that are definitely neurotoxic (e.g., thalidomide), probably due to species-specific characteristics of their toxicity.

Among the substances able to damage the PNS, several medications have been identified, with a particular relevance for anticancer drugs (Table 20.1). However, alcohol is a frequent cause of neuropathy (despite the pathogenesis of alcohol-related neuropathy is still debated and a role of nutritional deficiency cannot be ruled out) and environmental as well as industrial toxics can target the PNS.

Table 20.1 Medications associated with peripheral neurotoxicity

Anticancer drugs	Cardiovascular agents	Antibiotics/antivirals	Miscellaneous agents
Alemtuzumab	**Amiodarone**	**Chloroquine**	**Colchicine**
Bortezomib	**Perhexiline**	**Dapsone**	**Dichloroacetate**
Brentuximab vedotin	Clofibrate	**Isoniazid**	**Disulfiram**
Epothilones	Flecainide	**Linezolid**	**Etanercept**
Platinum compounds (cisplatin, carboplatin, and oxaliplatin)	Hydralazine	**Metronidazole**	**Infliximab**
Suramin	Procainamide	**Nucleoside analogues**	**Pyridoxine excess**
Taxanes	Propafenone	**Nucleoside reverse transcriptase inhibitors (NRTI)**	Acitretin
Thalidomide	Statins	Chloramphenicol	Allopurinol
Vinca alkaloids		Ethambutol	Almitrine
5-Azacitidine		Fluoroquinolones	Botulinum toxin
5-Fluorouracil		Griseofulvin	Cyclosporin A
Clioquinol		Nitrofurantoin	Gold salts
Cytarabine		Podophyllin resin	Interferons: alfa2a, alfa2b
Etoposide (VP-16)			Leflunomide
Gemcitabine			Lithium
Hexamethylmelamine			Nitrous oxide
Ifosfamide			Penicillamine
Misonidazole			Phenytoin
Teniposide (VM-26)			Sulfasalazine
			Tacrolimus
			Zimeldine

Bold = drugs with established peripheral neurotoxicity

20.2 Drug-Induced Peripheral Neurotoxicity

In the case of drug-induced PNS damage, the term "neurotoxicity" is more appropriate than the commonly used "neuropathy" because DRG neuronal and glial targeting is frequently a major event beyond peripheral nerve damage. Among the drugs with a well-established neurotoxicity, antineoplastic, antiarrhythmic, and antiretroviral agents have been described.

20.2.1 Antineoplastic Drugs

Several classes of effective antineoplastic drugs are severely neurotoxic (Fig. 20.1), and some of these compounds are still used in the treatment of the so-called big killers, i.e., lung, breast, and gastrointestinal cancers. This widespread clinical use leads to millions of subjects to be potentially exposed worldwide to the risk of developing chemotherapy-induced peripheral neurotoxicity (CIPN) [5–7]. Platinum drugs, antitubulins, proteasome inhibitors, and antiangiogenic anticancer drugs have all been reported to cause severe CIPN. However, even the "targeted therapies" (i.e., new drugs able to specifically damage cancer targets) are not free from off-target side effects, including peripheral neurotoxicity [5].

The fundamental mechanisms of CIPN are only scarcely known, but it is now widely accepted the concept that these mechanisms do not perfectly overlap with those exploited by these drugs to exert their anticancer activity. Except for vinca alkaloids and thalidomide, clear DRG damage has been demonstrated at the pathological level in relevant animal models [8, 9]. Platinum drugs are able to interact with the nuclear DNA of highly replicating cancer cells, thus limiting their capacity to complete mitosis and inducing apoptotic cell death. This mechanism is unlikely to be relevant in nonreplicating neurons, although using very high doses of cisplatin apoptosis can be induced also in neurons, and an indirect effect on glial cells cannot be completely ruled out by the available preclinical data. Therefore, a number of studies have been performed in order to identify alternative pathogenetic mechanism of the toxicity of platinum drugs, including increased oxidative stress and mitochondrial damage [10]. Besides their known effect as microtubulin stabilizers, mitochondrial damage has also been suggested to explain the neurotoxicity of taxanes and that of bortezomib, the first proteasome inhibitor entered in clinical practice. However, an effect on tubulin has also been demonstrated for bortezomib, and this might be relevant to explain its peripheral neurotoxicity [11]. Vinca alkaloids capacity to disrupt the cytoskeleton is likely to be the main mechanism of axonal damage, while epothilones probably share the same mode of action of taxanes, at least on microtubules. So far, no explanation has been provided for the peripheral neurotoxicity of thalidomide. Selective accumulation of antineoplastic drugs into DRG neurons could result from the presence on their plasma membrane of transporters able to carry them into the cell cytoplasm [12], thus mimicking a mechanism already described to explain cisplatin nephrotoxicity [13, 14].

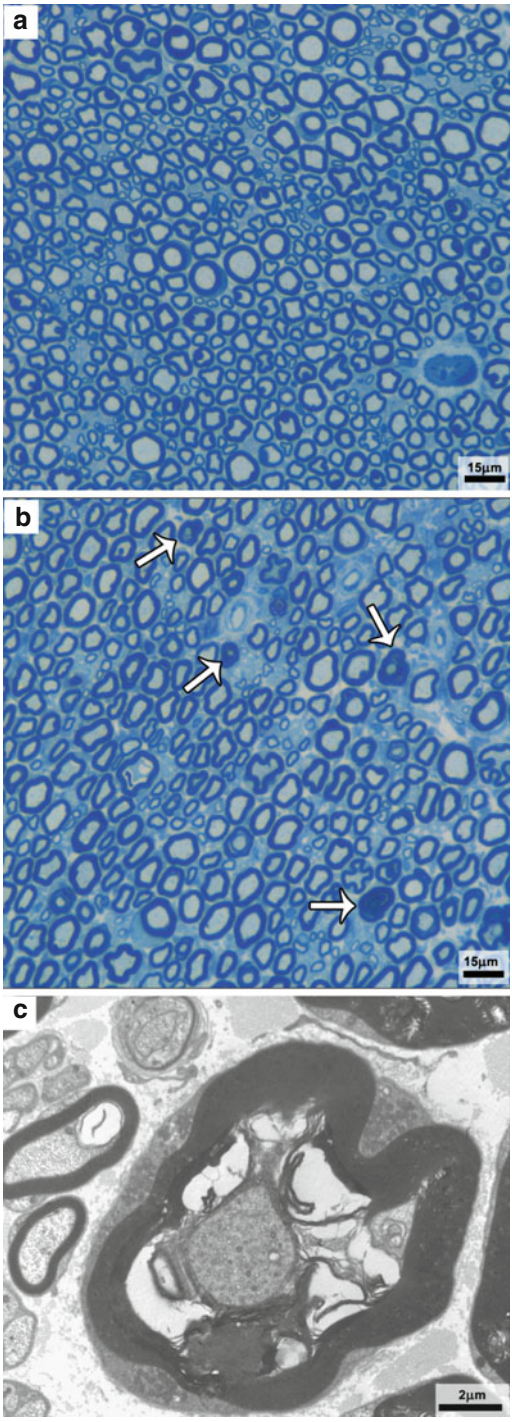

Fig. 20.1 Comparison between the histological features of the sciatic nerve of a control rat (**a**) and of an animal chronically treated with paclitaxel, the first-in-class taxane (**b**). The density of myelinated fibers is clearly reduced and fibers undergoing active Wallerian-like degeneration are evident (*arrows*). The ultrastructural examination confirmed the active degeneration of axons. (**a**, **b** toluidine blue staining of epoxy resin semithin sections; **c** uranyl acetate/lead citrate staining of osmium tetroxide postfixed epoxy resin ultrathin sections)

Platinum drugs induce a chronic, sensory neuropathy, which might lead to disabling ataxia in the most severely affected subjects. Only oxaliplatin can also present an acute neurotoxicity, with cold-induced paresthesias and cramps. Sensory symptoms are also largely predominant with all the other antineoplastic drug, although the clinical spectrum is different. Neuropathic pain is prominent in bortezomib-treated patients, and a painful syndrome is also frequent after taxane administration, where distal motor impairment can be present. Autonomic dysfunction is the most worrisome toxic effect in patients treated with vinca alkaloids, particularly vincristine. Motor impairment is very rare after thalidomide administration. In all the cases of CIPN with a regular clinical course, the use of neurophysiological assessment is relatively non-informative, and axonopathy is the common feature [5].

The neurotoxicity of "targeted drugs" is less well known, although it is now clear that peripheral neurotoxicity can also result from the use of these drugs and can be severe. Interference with the immune system has been advocated as a possible pathogenetic event. Cases of acute inflammatory polyradiculoneuropathy have been reported in alemtuzumab-treated patients [15], and it has been hypothesized that alemtuzumab may trigger an autoimmune cascade resulting from indiscriminate dysregulation of regulatory T cells or through a molecular mimicry. The administration of brentuximab vedotin can be associated with a dose-dependent peripheral neuropathy, probably associated with unconjugated microtubule inhibitor monomethyl auristatin E (i.e., the active part of the molecule acting as the classical chemotherapy drugs). Despite generally peripheral nerve sensorimotor neuropathy being mild to moderate, dramatic motor neuropathy has also been associated with brentuximab vedotin use [16].

20.2.2 Antiarrhythmic Drugs

The use of several antiarrhythmic drugs such as propafenone, flecainide, and procainamide is reported to be associated with the onset of peripheral neuropathy, but the number of cases described is very low. Amiodarone, a highly effective drug used in the treatment of atrial fibrillation and ventricular arrhythmias, has several neurological and non-neurological toxicities, including tremor, ataxia, encephalopathy, parkinsonism, optic nerve damage, and myopathy. Besides these toxicities, peripheral nerve damage has also been described as one of the commonest neurological toxic effects of amiodarone. Since amiodarone neurotoxicity is time and dose related, its real incidence was probably overestimated in the earliest reports due to the high dose of the drug received by the treated subjects, while maintenance dose nowadays is much lower, and in a retrospective study, the overall incidence was 2.8 % with only a few cases of confirmed peripheral nerve damage [17]. The typical pathological features of amiodarone-induced neuropathy are lamellated inclusions particularly evident in the cytoplasm of Schwann cells, associated with secondary myelin changes. It is likely that these alterations (similar to those observed in perhexiline or chloroquine neuropathy) are due to drug-induced inhibition of lysosomal

phospholipases, leading to the formation of these lysosomal bodies in many cells types. A peculiar aspect of amiodarone is its very long elimination half-life (around 58 days as an average) so that a complete washout requires months after drug withdrawal. Amiodarone-induced neuropathy is a distal, sensorimotor neuropathy frequently associated with aching pain, a symptom which may help in the differential diagnosis with neuropathy due to hypothyroidism in patients suffering from amiodarone-induced thyroid gland dysfunction.

20.2.3 Antiretroviral Drugs

Mitochondrial DNA replication requires the function of DNA polymerase γ, and this enzyme can be inhibited by some of the nucleotide reverse transcriptase inhibitors (NRTI) which are used as component of the highly active antiretroviral therapy (HAART) for HIV-infected patients. Although replacement of dideoxyinosine, zalcitabine, stavudine, and lamivudine (the NRTI which are commonly associated with peripheral neuropathy) is generally implemented in the USA and Europe, they are still used for patients intolerant or non-eligible for other treatments and are also a fundamental treatment in most low-income countries. Patients with NRTI-induced peripheral neuropathy present with a distal, symmetrical painful sensory neuropathy, with mild or absent motor impairment, due to axonal damage and associated with mitochondria with clear alterations at the ultrastructural examination [18]. The cause of the specific selectivity of axons with preservation of Schwann cells is unknown, but it has been reproduced in vitro, where inhibition of mitochondrial transmembrane potential has been demonstrated in neurons, but not in co-cultured Schwann cells, exposed to NRTI. Since NRTI- and HIV-related neuropathies are both severely painful, the differential diagnosis may be problematic, and onset (which is more subtle in the infectious form) is the main clinical clue to discriminate between them.

20.3 Alcohol-Related Peripheral Neuropathy

According to the World Health Organization (http://www.who.int/substance_abuse/facts/en/), on average every person in the world aged 15 years or older drinks 6.2 l of pure alcohol per year. The relationship between chronic alcoholism and peripheral neuropathy is frequent (25–66 % of exposed subjects) [19], and it was first reported in 1787 by Lettersom [20], who described the event as due to direct toxicity of ethanol. This pathogenetic hypothesis resisted substantially unchallenged until 1928, when a possible alternative explanation for alcohol-related neuropathy was suggested based on the similarities observed with beriberi neuropathy caused by thiamine deficiency. Over the following years, clinical as well as animal studies strengthened the "thiamine hypothesis," but the lack of consistent positive results after thiamine supplementation raised some concern on the real extent of involvement of the vitamin in the onset of peripheral nerve damage in chronic alcohol

misusers. More recent studies compared the features of peripheral neuropathy in patients with demonstrated vitamin deficiency, and they concluded that the clinical picture and course as well as measured vitamin levels (including thiamine) were sufficiently dissimilar to suggest that the pathogenesis should be different [21]. The typical clinical features of alcohol-related neuropathy are represented by slowly progressive, distal, symmetrical neuropathy, predominantly involving sensation perception and autonomic function, in most cases with an important painful component. The neurophysiological correlates of these clinical features are represented by slowing in motor and sensory nerve conduction with marked reduction of potential amplitudes, which are consistent with the pathology results evidencing axonopathy.

20.4 Environmental and Industrial Toxics

20.4.1 Organic Solvents

Organic solvents, able to induce peripheral nerve damage, comprise a wide range of compounds, including n-hexane, styrene, toluene, trichloroethylene, and methyl-n-butyl ketone. Axonal swelling with accumulation of neurofilaments has been reported as the hallmark of hexacarbon-induced PNS damage, although demyelinating features can also be detected by the neurophysiological examination. Chronic, subacute sensorimotor neuropathy is the most typical clinical presentation, but autonomic dysfunction has also been described, as well as the association with encephalopathy and myelopathy. Occasionally, also cases of recreational exposure have been reported in "glue sniffers" [22]. Rapid onset of peripheral neuropathy has been more commonly reported in glue sniffers than in subjects exposed to chronic industrial intoxication, and coasting can occur after the removal from toxic exposure.

20.4.2 Industrial Chemicals

Carbon disulfide and acrylamide are among the most extensively studied industrial chemicals able to induce PNS damage. It has been estimated that only in the USA more than 30 million kilograms of carbon disulfide are released in the atmosphere each year during production of cellophane and rayon. Exposure to carbon disulfide induces an axonopathy affecting preferentially the largest myelinated fibers, with accumulation of neurofilaments at the paranodal zone [23]. The clinical features of carbon disulfide-induced neuropathy are those of a distal, sensory neuropathy with limb weakness.

The water-soluble vinyl monomer acrylamide is widely used in chemical industries and is a by-product in some food preparations. Acrylamide is severely toxic on the cerebellar Purkinje cells and it causes axonal degeneration in sensory and motor nerves. In animal models, extensive swelling of the neuromuscular junction with

accumulation of neurofilaments, tubulovesicular profiles, and degenerated mitochondria has been described [3]. Axonal loss and denervation are confirmed by neurophysiological examination. At onset distal sensory impairment is present in hands and feet, then autonomic dysfunction may appear and only mild motor impairment is generally present during the course of the neuropathy, which is slow.

20.4.3 Heavy Metals

Several heavy metals including lead, manganese, organic tin, mercury, arsenic, and thallium can cause peripheral neuropathies.

Chronic arsenic poisoning mostly results from consumption of contaminated ground water, particularly in Asia, secondary to natural sources and anthropogenic activities, e.g., mining or pesticide use [24]. In Western countries, cases of arsenic neuropathy have been reported to be occasionally associated with the consumption of contaminated dietary supplements or seafood, and acute neuropathy mimicking Guillain-Barrè syndrome has been reported after use of herbal medicines [25]. Peripheral neuropathy is not among the most frequent toxicities of arsenic being present in approximatively 5–10% of chronically intoxicated people. The usual clinical presentation is represented by distal sensory loss with mild weakness secondary to predominantly axonal damage. Cerebrospinal fluid examination can show mild hyperproteinorrachia, and skin changes are present in chronically exposed subjects, thus providing useful clues to the diagnosis which should be confirmed with specific urine search.

Environmental and industrial exposures are also the main reasons for mercury intoxication. The outbreak of methylmercury poisoning in Minamata Bay (Japan) in the 1950s allowed to clearly establish the hallmark lesions in the anterior portion of the calcarine cortex and depletion predominantly of granular cells in the cerebellar cortex, but these patients had also evidence for a sensory neuropathy affecting the distal extremities. Pathological studies evidenced endoneurial fibrosis, fiber loss, Büngner's bands, and regenerated myelin sheaths. Subacute mercury-induced neuropathy is predominantly motor, while chronic neuropathy is sensorimotor. The real extent of peripheral nerve damage can be masked by the concomitant presence of signs of central nervous system damage [26]. Urine examination can confirm the diagnosis in suspected cases. The claim that the use of mercury-containing dental amalgams could be associated with increased risk of neurological toxicities, including peripheral neuropathy, has never been supported by firm scientific evidence [27].

Lead is one of the major pollutants accumulated in our environment over the centuries. It has been calculated that there has been a 100-fold increase in the amount of lead accumulated in the human skeleton bones over the last 5000 years [28]. The use of lead is surpassed only by ferrous metals (e.g., the use of lead-based fuels, manufacture of batteries, crushing and smelting of lead-containing residues, technology industry). Despite strict regulations at least in developed countries, subacute intoxication is in the vast majority of cases due to unprotected industrial

exposure and produces motor impairment of variable severity, frequently asymmetrical and described to involve the hands and finger extension before spreading to other districts, including cranial nerves. Chronic, low-intensity exposure is generally associated with sensorimotor impairment. Association with gastrointestinal symptoms (e.g., constipation, abdominal pain) is fairly common and may direct the diagnosis. Axonal damage is the pathological hallmark of lead-induced neuropathy in humans, although demyelination has been observed in animal models. It has been proposed that lead can induce peripheral nerve damage through interference with porphyrin metabolism and mitochondrial toxicity [28].

Key Point Box

- The peripheral nervous system is frequently targeted by toxic agents.
- Several widely used medications are toxic on the peripheral nervous system.
- Environmental and industrial exposure to neurotoxic agents is still relatively frequent, and it can be difficult to detect.
- Recreational abuse substances besides alcohol are neurotoxic.
- Sensory impairment is generally predominant over motor or autonomic damage.
- The clinical course is highly variable and "coasting" can occur.

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