Multifocal Motor Neuropathy: Update on Clinical Characteristics, Pathophysiological Concepts and Therapeutic Options

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Key Words

Multifocal motor neuropathy • Conduction block •
Anti-GM1 antibodies • Ion channels

Abstract

Multifocal motor neuropathy (MMN) is an acquired immune-mediated neuropathy characterized by chronic or stepwise progressive asymmetrical limb weakness without sensory deficits. The upper extremities are more often affected than the lower extremities with distal paresis dominating over proximal paresis. Important diagnostic features are persistent multifocal partial conduction blocks (CBs) and the presence of high-titer anti-GM1 serum antibodies. Motor neuron disease, other chronic dysimmune neuropathies, such as chronic inflammatory demyelinating polyneuropathy and the Lewis-Sumner syndrome (MADSAM neuropathy), are important differential diagnoses. While corticosteroids and plasma exchange are largely ineffective, high-dose intravenous immunoglobulins are regarded as first-line treatment. In spite of significant success in elucidating the underlying disease mechanisms in MMN during the past few years, important pathophysiological issues and the optimum long-term therapy remain to be clarified. The present review summarizes the clinical picture and current pathophysiological concepts of MMN with a special focus on the molecular and electrophysiological basis of CBs and highlights established therapies as well as possible novel treatment options.

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Introduction

More than 20 years ago Roth et al. [1] reported a patient with chronic asymmetric, distal motor neuropathy without sensory loss. Electrophysiological examination revealed proximal multifocal persistent conduction blocks (CBs) outside the common entrapment sites. Soon afterwards, others described individuals with similar characteristics [2, 3]. The term ‘multifocal motor neuropathy’ (MMN) was coined in 1988 by Pestronk et al. [4] who first recognized the association of MMN with anti-GM1-IgM antibodies and the responsiveness to immunomodulating therapies. Since then, systematic clinical and electrophysiological evaluation of larger patient cohorts increased our pathophysiological understanding of MMN and paved the way for more effective treatments [5–10]. Especially the successful application of intravenous immunoglobulins (IVIg) marked a cornerstone in MMN therapy and is nowadays regarded as the gold standard [10–16]. More recently, diagnostic criteria for this rare neuropathy have been proposed by various European and American neurological associations [17, 18] which help to delineate MMN from other neuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP) or multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy (Lewis-Sumner syndrome) and motor neuron disease (MND).

Although MMN has meanwhile been identified as a distinct nosological entity and significant success has

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been made in elucidating important aspects of the disease, several issues remain to be clarified. For example, there are still unsettled questions concerning the etiology of MMN, the biological basis of CBs as well as the optimum long-term therapy [8, 19–21].

Clinical Features and Disease Course

MMN is a rare disease with an estimated prevalence of 1–2/100,000 individuals. It is more frequent in men than women, with an approximate ratio of 3:1. The mean age at disease onset is 40 years. Almost 80% of the patients develop first symptoms between 20 and 50 years of age [7, 9]. Thus, MMN predominantly affects young people. Clinically, MMN is characterized by slowly progressive or stepwise progressive, asymmetric and distally accentuated paresis related to distinct peripheral nerves. The upper limbs are usually affected earlier and more severe than the lower limbs [6, 7, 22, 23]. In only 5–10% of all cases MMN manifests with proximal muscle weakness [9, 24]. The most common initial symptom is wrist drop and impaired grip strength. Muscle atrophy is often mild in the early stage, but may become prominent during the course of the disease when it is usually associated with a poor response to immunomodulatory therapy [13, 25]. Other symptoms comprise fasciculations and muscle cramps in about 50% of the patients, while myokymia has only been reported occasionally [1, 25]. Another characteristic that defines MMN is the absence of sensory symptoms. Only a few patients complain of discrete paresthesia or numbness during the course of the disease, and a minor loss of vibration sense has been documented in 20% of the subjects [7, 9]. Tendon reflexes from the paretic muscles are usually reduced but may be normal or even, though rarely, brisk. In the latter case, differentiation from amyotrophic lateral sclerosis or lower motor-neuron disease can be difficult. Cranial nerve involvement is uncommon and, if present, predominantly affects the N. Hypoglossus [26, 27].

Most patients develop a slowly progressive disease course in which the degree of disability correlates with the overall duration of the disease [28, 29]. Besides, relapsing forms of MMN showing acute deterioration, stepwise progression, as well as spontaneous remissions have occasionally been described [2, 13, 30]. Anecdotic reports on subacute monophasic MMN presenting with tetraparesis, preserved tendon reflexes and normal motor and sensory nerve conduction following *Campylobacter jejuni* infections [31–33] most likely reflected aberrant forms

of Guillain-Barré syndrome (GBS) [34]. Although the prognosis *ad vitam* is favorable and only 2 fatal cases have been directly ascribed to MMN after several years of disease [3, 27], the majority of patients accumulate significant disability as a result of severe paresis. Moreover, pathological fatigue was only recently highlighted in MMN [28, 35, 36].

Pathophysiology of MMN

Molecular Basis of Conduction Block

The electrophysiological hallmarks of MMN are CBs (see ‘Electrophysiological Findings’ below) which are supposed to be the underlying cause of muscle weakness. However, patients exist who present with clinical symptoms typical for MMN but in whom CBs cannot be detected by routine neurography. Here, very proximal or distal CBs inaccessible to standard neurography might be present [16]. Interestingly, the majority of nerve-conduction studies in MMN demonstrated significant improvement of CBs after treatment with IVIg, although muscle strength in these patients rarely recovers to normal [10].

In general, CB appears when the incoming action current at the node of Ranvier is unable to induce sufficient depolarization at the subsequent node to generate an action potential [37, 38]. Experimental paranodal demyelination in rodents severely impaired saltatory nerve conduction suggesting that focal demyelination is the pathological basis of CB [23, 39]. This hypothesis was further strengthened by morphological nerve studies confirming circumscribed demyelination in biopsies from MMN patients [38–41]. Beyond focal demyelination, generalized axonal dysfunction might be present in MMN [42]. Pathological and electrophysiological findings have highlighted the functional role of axonal disintegration and impaired axon-myelin interactions [41, 43–46]. The question whether axonal degeneration is an intrinsic pathophysiological feature of MMN or caused by persistent CBs is still under debate. Recent studies point out that activity-dependent processes can induce CB-induced axonal degeneration. According to this, the axonal membrane hyperpolarizes at the vicinity of a CB due to altered K^+ conductivity [42], but depolarizes at the site of CB through inhibition of the Na^+/K^+ -ATPase caused e.g. by edema, reduced oxygen supply or immune-mediated mechanisms such as binding of autoantibodies [38, 46] (fig. 1A, B). This scenario is further aggravated by disruption of the blood-nerve barrier leading to increased K^+ concentrations in the endoneural fluid hence further

Fig. 1. Possible molecular mechanisms of CB and axonal degeneration in MMN. **A** Edema formation, restricted O_2 diffusion and/or antibody-mediated processes following focal demyelination can cause inhibition of Na^+/K^+ pumps. This then leads to an increase in intracellular Na^+ and, according to the electrogenic nature of the $\text{Na}^+/\text{K}^+\text{-ATPase}$, to depolarization of the membrane potential. Significant depolarization finally presents as CB. **B** Lo-

cally increased Na^+ concentrations at the site of CB form a Na^+ gradient at the vicinity of CB. This scenario activates Na^+/K^+ pumps (increased 'driving force') accompanied by membrane hyperpolarization. **C** Persistent CB can saturate the activity of the sodium-transporting machinery, hence reversing the function of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger. As a consequence, Ca^{2+} accumulates in the axon and finally causes axonal degeneration.

supporting accumulation of intracellular Na^+ ions and membrane depolarization. Persistent Na^+ influx can only be counterbalanced by Na^+ ions moving intracellularly along the axon to a site where the Na^+/K^+ pump is still functional. As a consequence, the Na^+ gradient from the lesion site to the distal part of the nerve is decreased [46] (fig. 1B). Raised intracellular Na^+ concentrations are the 'driving force' for the $\text{Na}^+/\text{K}^+\text{-ATPase}$ resulting in increased pump activity and membrane hyperpolarization [47–49]. According to this pathophysiological concept, ongoing CB would trigger sustained elevation in intracellular Na^+ . Under these conditions the activity of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger ($3 \text{ Na}^+ / 1 \text{ Ca}^{2+}$) can be reversed [44–46, 50] leading to intra-axonal accumulation of Ca^{2+} and subsequent axonal degeneration (fig. 1C).

Immunopathogenesis of MMN

There are several arguments for MMN being an immune-mediated disease [5, 6, 25]: anti-GM1 antibodies are found in 20–80% of patients suffering from MMN, and GM1 is expressed on axons and the myelin sheath. Interestingly, the molecular composition of GM1 differs between sensory and motor nerves resulting in different binding affinities of anti-GM1 antibodies hence, offering a possible explanation for the selective impairment of motor fibers in MMN [51–53]. Moreover, many MMN patients respond to immunomodulatory treatment. Finally, highly specific therapies that selectively interfere with the immune system such as $\text{TNF}\alpha$ antagonists (infliximab) can induce MMN in rare cases [54]. Similar to other neurological disorders associated with serum anti-

bodies the question arises whether anti-GM1 antibodies in MMN are pathologically relevant or represent a mere epiphenomenon. Indeed, previous studies reported anti-GM1-mediated focal demyelination and blockade of voltage-dependent Na^+ channels at the node of Ranvier in vivo and in vitro [55–57], but these findings could not be confirmed by others [58–60]. Although human IgM anti-GM1 antibodies can act on voltage-gated Ca^{2+} channels in vitro, the significance of this interaction for the pathogenesis of MMN remains unclear [61]. The remarkable proportion of anti-GM1 antibody-negative patients (up to 50%) who, in comparison to anti-GM1-positive individuals, similarly respond to IVIg argues against an exclusively antibody-mediated disease mechanism [12, 25, 62, 63]. Along these lines motor-nerve conduction in mice could be blocked by human serum samples devoid of anti-GM1 antibodies indicating that other soluble mediators are pathogenetically relevant in MMN [10, 64]. Finally, IVIg treatment, although clinically effective, does not reduce anti-GM1 titers [4, 65].

Taken together, the exact immune mechanisms operative during MMN are still unknown and the available data can currently not prove or disprove a causative pathogenetic role of anti-GM1 antibodies [64].

Diagnostics of MMN

Electrophysiological Findings

The most prominent electrophysiological features in MMN are multifocal, persistent, partial CBs present in motor but not sensory nerve fibers and located outside the common entrapment sites [3, 12, 66, 67] (see ‘Molecular Basis of Conduction Block’ above). In general, CB has been defined as the reduction of the amplitude or area under the curve of the compound motor action potential (CMAP) on proximal compared to distal nerve stimulation. However, consensus on the required magnitude of amplitude or area reduction that unambiguously defines partial CB has not yet been reached. This is mainly due to the fact that besides CB, several other mechanisms can lead to significant CMAP reduction (‘pseudo CB’). Because axons of a chronically demyelinated nerve display different conduction velocities (known as temporal dispersion, TD), the positive phase of the fast motor-unit action potentials overlaps with the negative phase of slow motor-unit action potentials (a phenomenon called ‘interphase cancellation’), resulting in a disproportionate proximal CMAP that can mimic true CB [68–71]. TD is common in chronic demyelinating disorders of the pe-

ripheral nervous system, such as CIDP or polyneuropathy associated with IgM gammopathy. In addition, collateral nerve sprouting present for example in MND increases the rate of polyphasia and reduces CMAP amplitudes [72, 73]. Finally, technical limitations such as insufficient supramaximal stimulation of the proximal nerve segments can lead to pseudo-CB.

The degree of CMAP reduction necessary to define partial CB in MMN varies considerably between different studies, ranging from 20% to more than 50% with a maximum admissible TD between 15 and 30% [7, 9]. A computer simulation study in rats, in which compound muscle-unit action potentials were reconstructed from motor-unit action potentials, showed that maximum TD can result in a decrement in the CMAP area of up to 50% [70]. A recent retrospective investigation in humans for the first time established simulation-based thresholds for CB in the forearm segment of the median nerve [23]. However, these thresholds still have to be evaluated for other nerves and validated in a prospective manner. Even in healthy individuals CMAP amplitudes are commonly lower after proximal compared to distal nerve stimulation with a range of reduction between 12 and 54% [74]. Given the results from the above-referenced studies, the commonly applied cutoff level of 50% CMAP decline (amplitude or area) is the most validated electrophysiological criterion of partial CB. Consequently, this threshold was chosen for the definition of definite partial CB in most of the peripheral nerves according to the consensus criteria of the American Association of Electrodiagnostic Medicine [18] and the European Federation of Neurological Societies/Peripheral Nerve Society (table 1). However, the 50% limit should not be applied if CMAP amplitudes are below 20% of the normal value. Then, potentials are often too polyphasic to allow proper quantification. The relatively restrictive American and European electrophysiological criteria aim to avoid confusion between real CB and TD, i.e. pseudo-CB. This approach, however, may lead to the underdiagnosis of MMN which represents a potentially treatable neuropathy [28, 67, 71, 75, 76]. Hence, it is important to bear in mind that a reduction in amplitude or area smaller than 50% might already represent partial CB, especially because CB, although considered to be persistent [73, 77], is a dynamic entity that changes over time [75], and a CMAP reduction of >50% may be preceded by a smaller decrease underlining the need for electrophysiological evaluation at regular intervals. Sometimes subtle focal CB can be detected using the so-called ‘inching technique’ where several nerve sites with an interstimulation distance of 10–15 mm are

stimulated sequentially [78, 79]. Here, an abrupt and circumscribed reduction in CMAP amplitude differentiates focal CB from pseudo-CB which, in contrast, is characterized by a more gradual CMAP decrease with increasing stimulation distances. At the site of CB, conduction velocity in motor but not sensory fibers is usually significantly reduced. Moreover, one should bear in mind that the same nerve can be blocked at several sites [12, 67, 80].

It is important to note that CB is not specific for MMN but can also be found in several other neuropathies. In contrast to MMN, CB occurring during acute compressive neuropathy or hereditary neuropathy with liability to pressure palsies are located at common anatomical entrapment sites like the ulnar sulcus or caput fibulae while those present after ischemic nerve injury are transient and usually reversible [81, 82]. Patients suffering from GBS or CIDP in addition to CB regularly develop other electrophysiological signs of severe demyelination like markedly prolonged distal motor latencies or increased F-wave latencies [83, 84].

Another specific problem with the diagnosis of MMN is the detection of proximally located CB. Due to anatomical restrictions, the routinely used surface electrodes are not able to stimulate proximal nerve segments (plexus, nerve roots). This technical limitation can be overcome by the application of transcutaneous magnetic coils or high voltage stimulators [85, 86] which, however, can often not deliver the focal impulses necessary for the exact calculation of nerve conduction velocities or are inappropriate for supramaximal fiber stimulation [87]. Although F waves provide information on the integrity of a peripheral nerve over its whole course and, at least theoretically, should be an ideal tool for the detection of (proximal) CB, F-wave persistency depends on several other factors such as axonal integrity and its reduction does not necessarily indicate proximal CB [86]. Whether the recently reported 'magnetic fatigue test' in which activity-dependent CBs are unmasked by serial magnetic stimulation [88] can indeed delineate between true CB and the reduction of CMAP in MND needs to be further established. Finally, a novel approach using a triple stimulation technique to detect CB proximal to Erb's point might help to increase the diagnostic sensitivity in the future [89].

Although CB clearly is an important hallmark of MMN, the question whether its presence is mandatory for the diagnosis of MMN is still under debate [90]. About 30 cases of MMN with typical clinical presentation and a good response to IVIg but without CB have been reported so far [4, 76, 91, 92]. In a recent retrospective anal-

Table 1. Electrophysiological criteria of definite CB according to the EFNS/PNS Joint Task Force [115] and the AAEM [87]

Nerve segment	Amplitude reduction ^a , %	Area reduction, %
Median nerve		
Elbow/wrist	>50	>40 (50)
Axilla/elbow	>50	>40 (50)
Ulnar nerve		
Elbow/wrist	>50	>40 (50)
Elbow prox./dist.	>50	>40 (50)
Axilla/prox. elbow	>50	>40 (50)
Peroneal nerve		
Dist. fibula/ankle	>60	>50 (50)
Fibula prox./dist.	>50	>40 (50)
Tibial nerve		
Knee/ankle	>60	>50

Values in brackets according to the EFNS/PNS Joint Task Force [115].

^a Not included in the EFNS/PNS Joint Task Force [115].

ysis, patients with and without CB showed similar clinical features and a comparable response to IVIg treatment after a median follow-up of 7 years, suggesting related, if not identical disease entities [93]. Final appraisal of the existence of CB-negative MMN is hampered in that it is not clear whether these subjects really never had CB or whether CB merely disappeared over time due to secondary axonal degeneration and subsequent reduction also of the distal CMAP amplitudes [22, 28, 94].

Other electrophysiological hallmarks in MMN apart from CB can comprise increased distal CMAP latencies and prolonged or absent F-waves both of which mainly result from mild demyelination [13, 67, 80, 95]. The clinical finding of severely paretic muscles but with preserved bulks and normal neurography from the corresponding nerves is suspicious for distally located CBs. Those can occasionally be confirmed by needle electromyography (EMG) when an increased motor unit discharge rate (>20 Hz) in the absence of spontaneous activity is found [74].

Laboratory Findings

The most common laboratory findings in MMN are IgM serum antibodies against the ganglioside GM1 [4] which can be detected at high titers in 30–80% of the patients [7, 9]. The reported variations in the incidence of GM1 antibodies are probably related to the different ELISA assays used in the different studies as well as heterogeneous control populations [27, 96–99]. Besides

GM1 antibodies, immunoreactivity against other axon or myelin components such as the glycolipids GD1a or GM2 can be infrequently found [80, 100, 101]. The applicability of anti-GM2 antibodies for diagnosing MMN has recently been confirmed in a retrospective study including patients with different neuropathies [44]. Because glycolipids are presented to antigen-specific T cells by CD1 molecules expressed on the surface of various antigen-presenting cells, a possible association of MMN and other chronic immune-mediated neuropathies with gene polymorphisms coding for CD1A and CD1E was hypothesized but could not be confirmed [45]. Similar to CB, anti-GM1 antibodies are not specific for MMN. They also occur in 5–10% of patients with MND, other immune-mediated neuropathies (GBS, CIDP) and even in healthy individuals [102–105], although GM1 titers are usually lower under these conditions compared to MMN [22, 106]. Interestingly, anti-GM1-antibodies of the IgG subclass are frequently found at high concentrations in patients with MADSAM neuropathy [107], GBS and MND [99]. Taken together, the detection of anti-GM1-IgM antibodies supports the diagnosis of MMN, while a negative finding does not exclude the disease.

Most routine laboratory parameters in MMN are normal. Muscle creatine kinase is supposed to be slightly elevated in about two thirds of the patients [28, 95]. However, this unspecific finding does not help to differentiate MMN from MND or other neuropathies. This is also true for analysis of the cerebrospinal fluid which, in most cases, shows a discrete increase in overall protein concentration (up to 80 mg/dl) but normal cell counts [108]. Serum electrophoresis might reveal elevated polyclonal antibody formation, while monoclonal peaks typical for IgM gammopathy are generally absent [4, 109].

Nerve Biopsy

Biopsies taken from sensory nerves (e.g. sural nerve) are naturally not helpful for the diagnosis of MMN and should only be performed if significant sensible deficits are present, and CIDP, Lewis-Sumner syndrome or vasculitis have to be taken into account. Accordingly, only a few reports on sensory nerve biopsies in MMN exist and those described either normal findings or unspecific signs of mild axonal degeneration, demyelination, or both, consistent with the infrequent sensory impairment in patients with MMN [79, 110]. Tissue samples taken from the motor nerves of MMN patients are likewise rare. Auer et al. [40] reported thinly myelinated axons and the formation of onion bulbs at the site of the suspected CB, which typically indicate simultaneous de- and

Table 2. Diagnostic criteria of MMN according to EFNS/PNS Joint task force [115] and AAEM [87]

Essential criteria for the diagnosis of definite MMN	
1	Slowly progressive or stepwise progressive asymmetric limb weakness related to at least two distinct peripheral nerves for more than 1 month (usually more than 6 months)
2	No objective sensory deficits except for minor vibration sense abnormalities in the lower limbs
3	Definite CB (table 1) in two or more peripheral motor nerves outside the common entrapment sites
4	Normal neurography from at least three peripheral sensory nerves
5	Absence of upper motor neuron signs (spasticity, clonus, bulbar symptoms, pyramidal tract signs)
Supportive criteria according to EFNS/PNS Joint Task Force [115]	
1	Predominant upper limb involvement at onset
2	Decreased or absent tendon reflexes in the affected limb
3	Absence of cranial nerve involvement
4	Cramps and fasciculations in the affected limb
5	Elevated IgM anti-ganglioside GM1 antibodies
6	MRI showing gadolinium enhancement and/or hypertrophy of the brachial plexus
7	Clinical improvement following IVIg treatment
Exclusion criteria	
1	Upper motor neuron signs
2	Marked bulbar involvement
3	Significant sensory impairment
4	Diffuse or symmetric pattern of paresis at the beginning of the disease
5	CSF protein >1 g/l

remyelination. In another study axonal degeneration outweighed myelin pathology, and onion bulb formation as well as para- and internodal demyelination were absent [111]. In contrast to CIDP, inflammatory cells invading the nerve are only sporadically found in MMN underlining that different disease mechanisms are functional [40, 43, 111].

Magnetic Resonance Imaging

About 40–50% of the patients with MMN show hyperintense signals on T2-weighted magnetic resonance imaging (MRI) or contrast-enhanced T1 sequences of the brachial plexus [112]. The pattern of signal alterations closely correlates with the distribution of muscle weakness [23, 28, 43, 112] and might colocalize with CB [43, 113]. Although these findings are unspecific and do not unravel the underlying pathology except for demonstrating edema and an impaired blood-nerve barrier, MRI

Table 3. Important differential diagnoses of MMN

	MMN	MND	CIDP	MADSAM neuropathy
Symptom pattern	Asymmetrical	Asymmetrical	Symmetrical	Asymmetrical
Sensory symptoms	No	No	Yes	Yes + pain
Tendon reflexes	Decreased	Increased	Areflexia	Decreased
Disease course	Slowly progressive	Rapidly progressive	Progressive/relapsing	Progressive/relapsing
CSF protein	<1 g/l	<1 g/l	>1 g/l	Rarely >1 g/l
IgM anti-GM1 antibodies	~30–50%	~10%	Rare	No
Response to IVIg	Yes	No	Yes	Yes
Response to steroids	No (worsening)	No	Yes	Yes

could become an elegant and noninvasive tool to assess the integrity of proximal nerve segments in the future. Since the pathological MRI signals in MMN are mainly asymmetrically distributed, this technique might in addition help to delineate MMN from similar entities such as CIDP in which signal alterations are usually symmetrical or MND showing normal MRI of the peripheral nervous system [112, 114].

Diagnostic Criteria and Differential Diagnosis

Several diagnostic criteria for MMN have been proposed since the first description of the disease [18, 28, 110, 115]. Most of them share similar features and are based on the characteristic clinical and electrophysiological findings. According to the American Association of Electrodiagnostic Medicine and the European Federation of Neurological Societies/Peripheral Nerve Society definite MMN requires slowly progressive or stepwise progressive asymmetric paresis related to two or more distinct peripheral nerves without objective sensory deficits (table 2). Clinical findings that exclude the diagnosis of MMN comprise upper motor neuron signs like spasticity, extensor plantar responses and bulbar palsy. Electrophysiological requirements are met if definite CB is detected within at least two different nerves outside the preformed entrapment sites.

The most relevant differential diagnoses are summarized in table 3. In contrast to MND, MMN is characterized by its mononeuritis multiplex-like distribution of muscle weakness, which is not simply asymmetric but follows distinct peripheral nerves [2, 116–118]. Furthermore, the disease course in MMN is more protracted and bulbar symptoms are missing. Finally, severe muscle atrophy is less common in MMN at least during early stag-

es. In line with this, spontaneous activity in EMG is more pronounced and widespread in MND including, e.g. paraspinal muscle groups. However, discrimination between MMN and ‘lower motor neuron disease’ presenting without upper motor neuron signs is often difficult on a mere clinical basis. Here, detection of CB and the presence of anti-GM1 antibodies can be helpful. Patients suffering from chronic polyneuritis predominantly develop sensory symptoms and symmetric muscle weakness which is accompanied by reduced or absent tendon reflexes. Electrophysiological findings are characterized by significant demyelination of both, motor and sensory nerves and the symptoms are often relapsing-remitting [19, 25, 119]. The distinction of MMN from Lewis-Sumner syndrome (MADSAM neuropathy) [77, 120] often appears a difficult challenge. MADSAM neuropathy is also a multifocal neuropathy with CB but, in contrast to MMN, significantly involves the sensory system and is often associated with neuropathic pain. Unfortunately, the extent of sensory deficits still consistent with MMN is not exactly defined [17, 18]. Therefore, the detection of reduced potentials in different sensory nerves by neurography is the most valid criterion that separates MADSAM from MMN. In addition, anti-GM1 antibodies are absent and cerebrospinal fluid protein is often elevated in Lewis-Sumner syndrome [118, 121]. Making the correct differential diagnosis is of more than academic interest because some patients with Lewis-Sumner syndrome respond to steroids, which are ineffective or even harmful in MMN patients (see below) [121, 122]. Whether it is really of clinical relevance to further separate pure MMN from MMN with sensory loss and MADSAM neuropathy clearly needs further evaluation [123]. Finally, acquired or hereditary entrapment neuropathies, e.g. hereditary neuropathy with liability to pressure palsies, should be taken into account [124]. These are often characterized by acute

and painful onset, and nerve damage is restricted to preformed anatomical entrapment sites (e.g. sulcus ulnaris, carpal tunnel).

Therapy

Because MMN is supposed to be an immune-mediated disease, various immunomodulatory treatment strategies have been applied to date in MMN patients. In contrast to CIDP and Lewis-Sumner syndrome, numerous studies have demonstrated that glucocorticosteroids and plasma exchange are ineffective in MMN. In fact, they even worsen the symptoms in up to 20% of MMN patients, underlining that different pathophysiological mechanisms must be functional [3, 4, 16, 85, 125, 126]. Nowadays, IVIg is regarded as first-line therapy and their efficacy in MMN has meanwhile been proven in 4 large double-blind, placebo-controlled trials [17, 23, 63, 127–129]. In addition, 2 retrospective trials confirmed that IVIg is initially effective in 70–86% of the patients by most individuals require periodic treatment for several years [130, 131]. Whether the subcutaneous route of IVIg administration is advantageous compared to regular intravenous infusions with respect to steady IVIg plasma concentrations, patients' quality of life or cost-effectiveness needs further evaluation [132–134]. Similar to other neurological disorders, the exact mechanism of action of IVIg in MMN is still unclear at present [135]. This also applies for the question whether patients with high titers of anti-GM1 antibodies respond better to IVIg compared to those with lower titers [7, 25, 95]. The clinical effect of IVIg is usually impressive and muscle strength improves substantially within the first week of treatment. Otherwise, the diagnosis should be reconsidered, although chronic paresis and muscle atrophy do not recover after IVIg application in most of the cases. While anti-GM1 antibody titers are not affected by IVIg and thus, are not suitable as therapeutic markers, disappearance of partial CB sometimes parallels clinical improvement [136–138]. The common IVIg dose at the beginning of the disease is 2 g/kg body weight given on 2–5 consecutive days. However, the treatment effect usually rapidly declines after several weeks. Therefore, it is important to find an applicable maintenance regime with individualized IVIg doses (e.g. 0.4 g/kg IVIg once weekly or 1–2 g/kg IVIg in monthly intervals) in order to optimize the cost-to-benefit ratio [62, 139]. Nevertheless the efficacy of IVIg decreases after several years of treatment in most of the patients, necessitating higher dosage or shortened infusion

intervals to stabilize the symptoms [94, 140]. The recent observation that higher doses of IVIg might be superior already at the initial stage [141] and be able to prevent secondary axonal degeneration or promote remyelination [142] needs to be confirmed in larger studies and valid data on the long-term efficacy of IVIg in MMN are missing.

Soon after the initial description of MMN, cyclophosphamide was tested for this indication in several small uncontrolled trials. Taken together, high doses of cyclophosphamide seem to have a moderate effect, especially when given intravenously while lower oral doses could not influence disease progression [4, 12, 26, 143]. Branagan et al. [144] recently reported a patient with refractory MMN who experienced sustained disease remission after high-dose cyclophosphamide (50 mg/kg body weight over 4 days) without stem cell rescue. In contrast, myeloablative cyclophosphamide followed by autologous stem cell transplantation worsened the symptoms in another patient [145]. Hence, further studies are clearly needed to finally judge the therapeutic potential of aggressive immunosuppressive regimens in MMN. Given its problematic risk-to-benefit ratio, cyclophosphamide is currently only recommended if IVIg is not sufficiently effective [17].

Many other immunomodulatory or immunosuppressive agents such as azathioprine, methotrexate, cyclosporin A, mycophenolate mofetil or β -interferons have occasionally been tested in MMN but in most cases revealed conflicting results and controlled trials on these substances are missing [3, 146–149]. Data concerning the efficacy of the monoclonal antibody rituximab, which targets the CD20 molecule on B cells and might be able to reduce pathological autoantibody levels in MMN, are likewise inconclusive and larger trials are needed [150–152].

Conclusion

During the past 20 years numerous clinical and electrophysiological studies have helped to shed light on the pathophysiology of MMN and led to significant advances in its diagnosis and treatment. IVIg can restore muscle strength and delay disease progression. However, therapies with proven long-term efficacy or even strategies able to cure the disease are still lacking underlining the need to continue the search for innovative treatment approaches. Although MMN is typically characterized by CB most likely caused by focal demyelination, the patho-

physiological abnormalities probably extend far beyond. Novel morphological and electrophysiological findings highlight the importance of axonal degeneration and impaired axon–myelin interactions, which probably occur already at early stages of MMN. Finally, anti-GM1 anti-

bodies seem to represent a valid diagnostic marker rather than the true trigger of the disease and other possible targets of the immune response in MMN await identification.

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