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Pathophysiology of Immune-Mediated Demyelinating Neuropathies — Part II: Neurology

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EDUCATIONAL OBJECTIVES Upon completion of this monograph, the reader will acquire skills to: (1) review the pathophysiology of Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, anti-myelin associated glycoprotein neuropathy, and POEMS syndrome and (2) recognize the pathophysiology of select immune-mediated demyelinating neuropathies.

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In this article we deal with the relationship between pathophysiology and symptoms and discuss the pathophysiology of specific disease entities, including Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, anti–myelin-associated glycoprotein neuropathy, and POEMS syndrome.

ABSTRACT: In the second part of this review we deal with the clinical aspects of immune-mediated demyelinating neuropathies. We describe the relationship between pathophysiology and symptoms and discuss the pathophysiology of specific disease entities, including Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), anti–myelin-associated glycoprotein (MAG) neuropathy, and the syndrome of polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS syndrome). The GBS subtypes acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN) will both be discussed, because their features overlap and AMAN also affects paranodal myelin and because their gangliosides have a slightly different dimension. However, the different ceramide portion lies in the bilipid membrane, whereas the ganglioside portion in motor roots contained more GM1 than sensory root fibers, suggesting that motor fibers are more vulnerable to anti-GM1 antibodies due to a higher amount of antigen. However, other studies did not confirm this difference.

Selective Involvement of Motor Nerve Fibers and Pure Motor Neuropathy. Selective involvement of motor axons at the peripheral nerve level, such as in MMN and AMAN, is not well understood, because individual peripheral nerve fascicles contain motor as well as sensory axons. The research to explain this selectivity was directed to differences in immunological and ion channel properties between motor and sensory fibers. One of the problems in immunological research is that motor and sensory axons can only be distinguished with certainty at the root level. With less certainty, peripheral nerve motor axons can be identified by staining of cholinesterase (ChAT), which is expressed on the axolemma of motor axons only. ChAT expression varies, however, so that motor axons with weak staining cannot always be distinguished from sensory axons that do not stain (reviewed by Castro et al.).

The amount of antigen may differ between motor and sensory axons. One study showed that human lumbar motor root fibers contained more GM1 than sensory root fibers, suggesting that motor fibers are more vulnerable to anti-ganglioside antibodies due to a higher amount of antigen. However, other studies did not confirm this difference.

Motor fibers may be targeted selectively because their gangliosides have a slightly different molecular composition than the same type of ganglioside in sensory fibers. The ceramide portion of gangliosides GM1, GD1a, and GD1b in motor roots contains fewer long-chain fatty acid chains than the ceramide portion in sensory roots. This difference, however, does not immediately explain selective motor involvement, because the ceramide portion lies in the bilipid membrane, whereas the antibodies bind to the extracellular sugar residues of gangliosides. However, the different ceramide portion in motor axons may change the 3-dimensional configuration of the extracellular sugar portion to make it more susceptible to anti-GM1 antibody binding. Several studies showed that
ganglioside GD1a is selectively targeted in motor fibers. Immunostaining of cross-sectioned fibers by high-affinity IgG anti-GD1a antibodies showed more prominent binding to human motor than to sensory roots, despite the finding that the quantitative GD1a content was similar in motor and sensory roots.8 Also, high-titer anti-GD1a antibodies from a patient with AMAN bound to the nodal region of human motor root fibers but not to that of sensory root fibers.10 Finally, motor axons in the phrenic nerve were more sensitive to GD1a-induced injury by membrane attack complex than sensory axons in the sural nerve.11 Other studies, however, did not support the predominant binding of anti-ganglioside antibodies to motor fibers. One study showed that anti-GM1 antibodies bound equally to motor and sensory root fibers, and another showed that anti-GM1 antibodies from a GBS patient bound more strongly to purified GM1 of sensory rather than motor roots.7,8 Differences in biophysical properties may render motor axons more vulnerable to conduction block than sensory axons when a mixed nerve is affected. Excitability studies have shown that motor axons have a smaller strength–duration time constant (SDTC) and larger rheobase than sensory axons.12 SDTC and rheobase are both derived from the relationship between current strength (I) and duration (t) of stimuli that evoke a predefined nerve response (e.g., a target compound muscle action potential of 50% of maximal). On empirical grounds, the I–t relation is hyperbolic, revealing that stimuli with smaller I values require larger t values (and vice versa) to evoke similar nerve responses. In the I–t relation, rheobase is the theoretical I needed to evoke the response if t is infinitely long, although it should be stressed that strength–duration properties are only valid for short-duration stimuli. SDTC, or chronaxie, is the value of t when I is twice rheobase. Because stimulus charge (Q = I · t), the I–t relation can be recalculated into a Q–t relation, which is linear and more convenient to analyze. SDTC is then given by the x-intercept and rheobase by the slope.13 SDTC reflects: (i) the small capacitance of the nodal membrane; and (ii) the amount of persistent Na+ current.

The smaller SDTC in motor axons reflects a smaller persistent Na+ current because the passive nodal properties are similar between motor and sensory axons.14 When the safety factor is reduced due to demyelination (Fig. 1A), conduction may be blocked in motor axons, but may just be maintained in sensory axons, because their relatively large persistent Na+ current contributes to excitability. The concept of safety factor was discussed in part I of this review1. Furthermore, the hyperpolarizing parts of threshold electrotonus and I/V relation reveal less hyperpolarization-activated cyclic nucleotide–gated (HCN) channel activity in motor than in sensory axons.15 Thus, when nerve pathology results in hyperpolarized axons, only motor axons may develop hyperpolarizing block.
because their hyperpolarization is less well counteracted by HCN channel activity. Finally, refractoriness, superexcitability, and subexcitability are all more pronounced in motor than in sensory axons.\(^1\,^{12}\) The mechanism of this difference is not well established, but as it concerns all recovery cycle parameters, its cause may lie in the initial event leading to the recovery cycle; that is, the first change induced by the action potential. A possible factor may be the longer duration of action potentials in motor versus sensory fibers, as demonstrated in the frog.\(^16\) The longer duration is due to a greater amount of transient, but slowly inactivating, \(\text{Na}^+\) current in motor nodes so that, for each action potential, more \(\text{Na}^+\) ions enter in motor than in sensory axons. It is unclear whether the difference in action potential size renders motor axons more susceptible to conduction block due to demyelination. On the one hand, short lasting nerve activity leads to summation of subexcitability, and as this is more pronounced in motor axons, short lasting activity-dependent hyperpolarization will therefore be greater and the safety factor smaller in motor versus sensory axons. On the other hand, the larger size of action potentials in motor axons is advantageous, as this contributes to the safety factor.

Rate-Dependent Block and Activity-Dependent Weakness. Decreased muscle strength in polyneuropathy is usually attributed to loss of axons or persistent conduction block. It is, however, difficult to ascribe weakness to one of these mechanisms, because both may occur in patients with immune-mediated demyelinating neuropathy. For instance, in a group of MMN patients, loss of axons and not conduction block was the single independent determinant for muscle weakness, despite the fact that all patients had evidence of conduction block.\(^17\) To complicate matters further, other mechanisms may give rise to weakness as well. Increased temporal dispersion may desynchronize activation of motor units, thereby impairing maximal force production.\(^18\) Sustained nerve activity may induce blocking in axons that were not blocked during short-lasting activity. The latter mechanism, discussed here, is known as rate-dependent block and may produce a temporary increase in weakness after exercise and possibly contribute to fatigue. When single demyelinated motor axons are stimulated for several minutes at non-physiological frequencies of 80–100 Hz, internodal conduction time gradually increases until conduction becomes intermittent or blocked.\(^19\) This rate-dependent block was also demonstrated during stimulation at frequencies of 10–50 Hz, which are in the physiological range for motor axons.\(^20,\,^{21}\) Because conduction failure occurred at interstimulus intervals that were considerably longer than the refractory period, another mechanism than that responsible for the refractory period must be involved.

Sustained firing of action potentials induces several changes, each of which may cause an additional reduction in the already diminished safety factor of demyelinated axons. Short trains of 10–20 impulses cause brief hyperpolarization, because the subexcitable periods after each action potential summate.\(^22,\,^{23}\) More prolonged repetitive firing may cause an increase in extra-axonal \(\text{K}^+\) concentration and lead to reduced \(E_k\) and depolarization that may first decrease threshold, but ultimately lead to \(\text{Na}^+\) channel inactivation and increased threshold (Fig. 1B).\(^24,\,^{25}\) Sustained firing also increases intra-axonal \(\text{Na}^+\) concentration, which produces a decreased \(\text{Na}^+\) concentration gradient, decreased \(\text{Na}^+\) influx during an action potential, and decreased driving current.\(^19\) The most important mechanism for rate-dependent block is hyperpolarization induced by increased activity of the electrogenic \(\text{Na}^+ /\text{K}^+\) pump. The latter arises because the pump is driven by the large amount of \(\text{Na}^+\) ions entering the axon during repetitive firing. The main arguments in favor of this mechanism are that blocking neither arose after replacement of \(\text{Na}^+\) ions by \(\text{Li}^+\) ions in the medium nor after topical application of the \(\text{Na}^+ /\text{K}^+\) pump blocker ouabain.\(^20,\,^{21}\) To depolarize these hyperpolarized axons to threshold, a larger-than-normal potential difference has to be overcome, which requires extra driving current. In the case of demyelination, this may not be available due to leakage of driving current so that conduction may become blocked. In normal subjects, maximal voluntary contraction induced excitability changes consistent with hyperpolarization (increased threshold, increased superexcitability, decreased SDTC), but also increased refractoriness immediately after maximal voluntary contraction that could not be explained by hyperpolarization.\(^26,\,^{27}\) The increased refractoriness was possibly related to transmission failure in distal axon branches.

In MMN and CIDP patients, rate-dependent block was sought by recording compound muscle action potentials (CMAPs) before maximal voluntary contraction and at several time-points thereafter.\(^28–31\) In 2 studies, a specially designed excitability protocol assessed threshold, superexcitability, and SDTC at 10-s intervals to allow for accurate following of membrane potential changes.\(^28,\,^{29}\) Maximal voluntary contraction induced a CMAP decrease lasting up to 3 minutes. In 1 patient, the CMAP evoked proximal to a demyelinating lesion...
was abolished temporarily after maximal voluntary contraction, whereas the distal CMAP remained unchanged.38 These findings were attributed to the previously described mechanism for rate-dependent block, because it was paralleled by changes in excitability indices consistent with rate-dependent hyperpolarization (increase in threshold and superexcitability, decrease in SDTC).

These studies suffered from methodological problems, however. In most patients, proximal CMAPs were evoked by magnetic cervical stimulation. This carries the risk of being submaximal, and the risk is increased further if activity has induced hyperpolarization of the axons under investigation. The CMAP decrease induced by maximal voluntary contraction may therefore be due to submaximal stimulation caused by hyperpolarization and not by rate-dependent block. Furthermore, criteria for rate-dependent block were not defined. Because maximal voluntary contraction also induces temporal dispersion of nerve action potentials, assessment of block from the summated activity of several axons, as is done in CMAP recording, requires criteria to distinguish temporal dispersion from block.30,32,33 Subsequent studies of a larger number of nerves in patients with MMN or CIDP employed supramaximal electrical stimulation up to the Erb point and adopted a predefined criterion for activity-dependent block that was based on simulations.32,35 The studies showed that maximal voluntary contraction induced increased segmental duration prolongation, indicating increased temporal dispersion. Rate-dependent block according to the predefined criterion was not observed, except in a nerve segment of a patient with CIDP. In agreement with these latter studies, high-frequency electrical stimulation of single sensory axons in CIDP patients induced slowing but no conduction block.34

A major problem in assessing rate-dependent block by means of CMAP recording is that maximal voluntary contraction may induce a CMAP increase that lasts several minutes. Previously this was only observed in normal subjects and patients with motor neuron disease, but not in MMN or CIDP.31 Subsequent studies, however, showed that it also occurred in many demyelinated and non-demyelinated nerves of MMN and CIDP patients.32,33 The most likely mechanism for the CMAP increase is that voluntary muscle contraction increases muscle Na⁺/K⁺ pump activity leading to muscle fiber hyperpolarization and larger muscle fiber action potentials.35

The findings just described raise doubt as to whether rate-dependent block is clinically relevant. In some single axon recordings it was only observed at axonal firing rates that do not occur in daily life. In clinical research, rate-dependent block was usually assessed after 1 minute of maximal voluntary contraction. Again, this hardly occurs in daily life, because forceful muscle contraction is usually maximal for only a few seconds.

Heat Block and Heat Paresis. It is well known that symptoms in multiple sclerosis may worsen after a hot bath.36 In demyelinating neuropathies similar effects were described. In a patient with CIDP, symptoms considerably increased during fever.37 Several studies indicated that this so-called “heat paresis” is likely caused by development of conduction block in demyelinated axons (heat block). In single demyelinated axons, conduction was blocked by a minor temperature increase of 0.5°C and was restored subsequently when temperature was decreased by 0.5°C.38 In 7 patients with various demyelinating neuropathies (CIDP, MMN, or ulnar nerve entrapment at the elbow) neurological deficits and signs of conduction block on conventional nerve conduction studies (NCS) increased after warming to 40°C and decreased after cooling to 20°C.39

Heat block is caused by the unfavorable combination of demyelination and temperature increase. Demyelination results in leakage of the driving current through the demyelinated part of the internode adjacent to the node-to-be-activated. This leakage leaves less driving current available to depolarize the node-to-be-activated. Temperature increase decreases amplitude and duration of the action potential at the active node so that the driving current at the node-to-be-activated decreases further.40 At critically demyelinated internodes, the additional reduction in the already diminished driving current decreases the safety factor below unity so that conduction will be blocked.

The decrease in action potential amplitude and duration occurring with temperature increase can be attributed to several factors. First, the time during which Na⁺ channels are open in response to depolarization (Na⁺ channel open time) is shorter. This is because the Q10 of the rate constant for activation of Na⁺ permeability is smaller than that for inactivation.41 Therefore, at higher temperatures, Na⁺ activation is slightly faster, but Na⁺ inactivation is markedly faster, resulting in shortened open time and, consequently, fewer Na⁺ ions entering the axon during an action potential. Ultimately, this mechanism may lead to some Na⁺ channels entering the fast inactivated state before they open.42 When, however, temperature in myelinated mammalian axons was raised from 20°C to 37°C, peak Na⁺ current did not decrease but increased slightly.43 This suggests that other mechanisms also affect driving current when
temperature is changed, such as alterations in leakage conductance, bilipid membrane structure, axonal resistance, and \( E_{Na} \). Second, the capacitive current leak across the internode increases with temperature, resulting in less driving current being available to depolarize the node-to-be-activated. Third, the rate constant \( z_n \) for fast K\(^+\) current activation increases more prominently with temperature than the rate constant \( z_m \) for transient Na\(^+\) current activation. This was shown for both axonal and muscle currents.\(^{44,45}\) It implies that an increase in temperature results in faster opening of both ion channel types, but that this effect is more prominent in K\(^+\) channels (which oppose the action potential) than in Na\(^+\) channels (which initiate the action potential). In normal mammalian myelinated axons, this difference in rate constants is irrelevant, because fast K\(^+\) currents are mediated by juxtaparanodal K\(^+\) channels. These are covered by myelin and therefore they have no role in action potential termination.\(^{46}\) When juxtaparanodal fast K\(^+\) channels are exposed by demyelination, however, they will contribute to action potential termination, and, because this contribution increases with temperature, they contribute to heat block.

The blocking temperature of demyelinated axons was shown to rise after application of 4-aminopyridine.\(^{47}\) This was attributed to an increase in safety factor due to augmentation of the driving current, because this was no longer counteracted by K\(^+\) channels exposed by demyelination.

In normal nerves the maximal conduction velocity increases approximately linearly with temperature over a wide range of temperatures until, at temperatures >45°C, conduction is blocked.\(^{48}\) This relationship is expressed by the ratio between conduction velocity increase (\( \Delta v \)) and temperature increase (\( \Delta T \)). For upper limb nerves \( \Delta v/\Delta T \) is approximately 2.2 m/s/°C.\(^{49}\) In experimental and human demyelinating neuropathies, however, the normal relationship between conduction velocity and temperature is lost, and \( \Delta v/\Delta T \) is decreased.\(^{50,51}\) Furthermore, the value of \( \Delta v/\Delta T \) decreases linearly with the conduction velocity at 37°C, so that markedly reduced conduction velocities hardly increase when temperature is increased. The relationships between the amount of demyelination, influence of temperature, and conduction velocity were simulated, but the determinants for the decrease in \( \Delta v/\Delta T \) were not elucidated.\(^{52}\)

### Cold Block and Cold Paresis

Complaints of increased weakness during cold were reported initially in a case of MMN.\(^{54}\) Subsequently, symptoms of cold paresis and heat paresis were analyzed by questionnaire in patients with MMN, CIDP, progressive spinal muscular atrophy (PSMA), and chronic idiopathic axonal polyneuropathy.\(^{55}\) Cold paresis was experienced by a proportion of patients in each group and was reported more frequently than heat paresis. Most importantly, symptoms of cold paresis occurred most frequently in MMN (83%), and the odds of experiencing cold paresis were 4–6-fold greater for MMN than for CIDP or PSMA patients. As this study only assessed subjective symptoms of weakness, it is necessary to perform force measurements to determine whether cold also induces an objective increase of weakness in MMN patients.

Although MMN is regarded as a disorder in which demyelination plays a role, cold paresis cannot be explained by the previously described demyelinating conduction block, as this should disappear in cold (see previous section on heat block). It was therefore hypothesized that cold paresis in MMN was not related to demyelination, but to inflammatory nerve lesions where axons are depolarized but just able to conduct impulses at ambient temperature. In these lesions, thermal reduction of Na\(^+\)/K\(^+\) pump activity due to cooling may induce additional depolarization and depolarizing block, because long-standing depolarization yields Na\(^+\) channel inactivation.\(^{54}\) The hypothesis predicts that the Na\(^+\)/K\(^+\) pump inhibitor digitalis will aggravate depolarization in MMN. In a patient with MMN, however, administration of digitalis resulted in paradoxical fanning-out of threshold electrotonus that is consistent with more hyperpolarization rather than depolarization.\(^{54}\) A possible explanation was that digitalis only gained access to the lesion site where the blood–nerve barrier is impaired and where it increased depolarization; at perilesional sites with intact barrier, electrogenic pump activity was increased to remove the increased Na\(^+\) load from the lesion site, yielding hyperpolarization.
Some steps of the hypothesis for cold paresis were supported by experiments. First, excitability studies revealed that stepwise cooling of the median nerve in normal subjects from 37°C to 25°C, 20°C, and 15°C resulted in progressive axonal depolarization that was best explained by thermal reduction in Na⁺/K⁺ pump activity. Muscle strength remained normal at 25°C, but decreased progressively with cooling from 20°C to 15°C, possibly due to impaired conduction in axons or muscle fibers. Second, animal models of inflammatory spinal root lesions indicated that inflammation may induce nitric oxide–mediated mitochondrial dysfunction, energy depletion of the ATPase-dependent Na⁺/K⁺ pump, and axonal depolarization. Third, in some nerves of MMN patients, axons may be permanently depolarized.

Alternatively, cold paresis may be due to cooling of muscle. In normal mammalian skeletal muscle fibers, cooling results in decreased availability of excitatable muscle Na⁺ channels (which are of the Nav1.4 subtype, having slightly different biophysical properties than the axonal Nav1.6 subtype), because the proportion of Na⁺ channels in the slow inactivated state increases with decreasing temperature. Among patients, two-thirds of patients with distal upper limb muscular atrophy (Hirayama disease) and 83% of patients with MMN reported cold paresis. Hirayama disease is a disorder that affects peripheral motor neurons in the anterior horn of the cervical cord and leads to denervation and weakness of hand muscles. NCS in 11 patients with Hirayama disease, and 1 patient with hypothermic atrophy due to ulnar neuropathy showed cold induced excessive conduction delay and waning of the compound muscle action potential during 20-Hz repetitive stimulation. These findings were attributed to increased sensitivity of reinnervated muscle fibers to develop depolarizing conduction block in cold. This mechanism may be related to the previously described increased proportion of muscle Na⁺ channels in the slow inactivated state. The possibility that this mechanism may also occur in MMN is supported by extensive needle electromyography studies in 20 MMN patients, which showed prominent signs of reinnervation consistent with collateral sprouting in most muscles. Also, pathological studies of motor nerves in MMN revealed prominent axon loss, which may have led to collateral sprouting and reinnervated muscle fibers.

FINDINGS IN PATIENTS

GBS: General. GBS is a self-limited acute neuropathy; it is characterized by flaccid paralysis, areflexia, ataxia, and sensory deficits that start 1–3 weeks after an infection and reach a nadir within 4 weeks. Recovery may be complete or partial. The subtypes of GBS include AIDP, AMAN, acute motor and sensory axonal neuropathy (AMSAN), acute sensory axonal neuropathy (ASAN), and Miller–Fisher syndrome. AIDP is the major subtype of GBS in Europe and North America, but it occurs more rarely in northern China and Japan, where axonal forms are found in up to 50% of patients. AMAN, AMSAN, and Miller–Fisher syndrome are associated with antibodies against peripheral nerve gangliosides.

Electrophysiology is an important clinical tool for distinguishing demyelinating and axonal subtypes, because it may reveal demyelination, loss of motor axons only, loss of sensory axons only, or mixed loss. Unfortunately, the interpretation of NCS in an acute neuropathy like GBS is not straightforward. First, in most criteria for GBS, except those described by Ho et al., conduction block is considered supportive of demyelination and AIDP. Short-lasting conduction block that resolves without temporal dispersion has also been observed in early stages of a GBS subtype associated with anti-ganglioside antibodies that resembled AMAN. This suggests that the block is due to nodal Na⁺ channel dysfunction rather than demyelination. Therefore, the finding of conduction block in itself cannot be attributed simply to a particular subtype. Second, classification depends on the timing of NCS relative to disease onset. Serial NCS lead to reclassification in as many as 40% of patients, especially from AIDP to an axonal form. Thus, classification may differ between studies that employ single or repeated NCS. Third, criteria for demyelinating slowing differ among studies so that they cannot always be compared. For motor conduction velocity (MCV) to be consistent with demyelination, values of 95%, 90%, 80%, 75%, and 70% of the lower limit of normal, and 60% of the normal mean, have been proposed for GBS. The 60% value is based on evidence obtained by determining the velocity that distinguishes hereditary axonal and demyelinating neuropathy or by assessing the slowest MCV in lower motor neuron disease and assuming that MCVs below this value reflect demyelination (reviewed by van Asseldonk et al.). Evidence for the other values cannot be found in the literature, although their diagnostic value was assessed by a posteriori evaluation of the sensitivity and specificity of entire criteria sets, in which MCV was a feature. This procedure is not suitable to assess cut-off criteria for a single NCS variable like MCV. There is, however, a need for liberal cut-off criteria, because the evidence-based criteria may be too strict to detect slight demyelination.

The cerebrospinal fluid (CSF) of patients with unspecified GBS was shown to contain the endogenous pentapeptide QYNAD that, when applied to...
rat sciatic nerve, induces acute conduction block on whole nerve recording. Application of QYNAD to neuron-like cells shifts the steady-state inactivation curve of whole-cell recorded Na\(^+\) currents to more hyperpolarized membrane potentials, indicating decreased availability of Na\(^+\) current over a range of membrane potential values. However, patch-clamping showed that QYNAD has no effect on currents generated by different Na\(^+\) channel subtypes, including Nav1.6, the most important subtype at the node of Ranvier. It is therefore unclear whether QYNAD contributes to impaired impulse propagation or clinical deficits.

**GBS: AIDP.** Postmortem studies in AIDP have shown multifocal T-lymphocyte infiltration in nerves and invasion of the myelin sheath by macrophages, yielding segmental demyelination and denuded axons. In severe lesions, axons are damaged as well. These findings may represent cellular immunity in which macrophages are targeted to antigens on the Schwann cell surface by T cells. Autopsy studies done in early stages of AIDP have shown activated complement and membrane attack complex on outer myelin layers prior to invasion of the myelin sheath by macrophages, and completely demyelinated axons were scarce. This suggests humoral immunity in early AIDP with binding of antibodies to Schwann cell epitopes and complement mediated myelin damage. The temporal evolution of GBS also suggests humoral, rather than cellular immunity. Antibodies against myelin protein zero (P0) or peripheral myelin protein 22 (PMP22) have been reported in AIDP, but only in a small proportion of patients. Anti-ganglioside antibodies were also reported in patients supposed to have AIDP but, as these cases were associated with Campylobacter jejuni infection or pure motor GBS, patients may actually have had AMAN. Increased endoneurial fluid pressure due to inflammation in nerve trunks likely contributes to the development of axonal degeneration in AIDP.

Electrophysiology performed within 2–15 days after onset may show motor conduction block or slowing consistent with stringent criteria for demyelination in approximately 60% of patients. Demyelinating NCS abnormalities become most prominent 4–8 weeks after onset, and recovery starts after 6–10 weeks. Conduction block resolves with appearance of CMAPs with slow initial components and increased duration on stimulation proximal to the site of block, consistent with remyelinating slowly conducting axons. This sequence also occurs with distally evoked CMAPs, indicating restoration of demyelinating conduction block in the segment between the distal stimulus site and the muscle. Axon loss, as revealed by persistent low distal CMAPs, may occur in severe cases.

Excitability indices have been found to be normal in AIDP. This finding was unexpected, because paranodal demyelination should have resulted in prolonged SDTC due to enlargement of the nodal area and because activity of exposed juxtaparanodal fast K\(^+\) channels should have limited superexcitability. Stimulus–response curves of motor axons were normal in AIDP. In another study using finer current-steps, stimulus–response curves were found to be abnormal, but the subtype of GBS was not specified.

Recordings from single cutaneous afferents during the recovery phase showed abnormalities that were restricted to patients with marked clinical sensory deficits. Furthermore, at least 50% of the units had to be abnormal before marked clinical symptoms occurred. Abnormal discharge patterns included solitary action potentials upon stimulation instead of bursts, failure to follow stimuli, and spontaneous activity; thresholds and conduction velocities were normal. It was suggested that the failure to react properly to stimuli reflected rate-dependent block due to demyelination or remyelination and that this failure contributed to clinical sensory symptoms and deficits.

**GBS: AMAN.** AMAN is associated with a preceding infection with *C. jejuni* and IgG antibodies against gangliosides. Antibodies are directed against GM1 in 64% of patients, GM1b in 66%, GD1a in 45%, and GalNac-GD1a in 39%. Sera of some GBS patients do not react with single gangliosides, but only with complexes consisting of 2 different gangliosides, suggesting that they form unique conformational epitopes. Reactive complexes have included GD1a/GD1b, GD1b/GT1b, GM1/GD1a, and GM1/LM1. AMAN is likely caused by antibodies against the bacterial wall of a specific genotype of *C. jejuni* that cross-react with these peripheral nerve gangliosides. Injection of rabbits with GM1 or GM1-like components of *C. jejuni* causes acute flaccid paralysis with anti-GM1 IgG antibodies and pathological findings that strongly resemble those in AMAN. This model is considered appropriate for the human disease. The association between *C. jejuni* infections and AMAN is strong but possibly not exclusive, because a small number of patients have an AIDP phenotype on electrophysiology.

Autopsy studies in fatal human AMAN showed nodal lengthening, nodal IgG and complement depositions, invasion of the space between nodes and Schwann cell processes by macrophages, and axonal degeneration; demyelination and...
lymphocyte infiltration were scarce. 79,95 These findings are consistent with antibody-mediated humoral immunity rather than with cellular immunity. It is likely that the Fc receptors of activated macrophages are targeted to autoantibodies bound to gangliosides on the axolemma. Although these findings prove that the immune attack is directed at the node, Schwann cells may possibly be involved as well, because their surface expresses a small amount of GM1.

NCS may show low CMAPs on distal stimulation and normal thresholds, which are usually interpreted as indicating permanent axon loss and poor prognosis. Serial studies, however, revealed that this vision needs to be modified. NCS performed in the first week of GBS with IgG anti-ganglioside antibodies showed decreased distal CMAPs, prolonged distal motor latency (DML), conduction block, and conduction slowing in forearm segments. 69,96 Thereafter, 2 patterns were observed. In some patients, distal and proximal CMAPs were persistently decreased as is consistent with axonal degeneration; these patients had a poor outcome. In other patients, however, DMLs and distal CMAP amplitudes normalized (indicating resolution of distal conduction block), and conduction block in the forearm disappeared without signs of temporal dispersion. These changes occurred within days after onset. Some patients were classified initially as having AIDP. The fast recovery was explained by temporary loss of nodal Na+ channel function related to the autoimmune process. 69 Remyelination was considered unlikely because, in AIDP, recovery is associated with appearance of increased temporal dispersion and starts after 6–10 weeks. 66 Axonal regeneration after distal degeneration of motor axon terminal branches was also considered unlikely, because this starts after 2–4 weeks. 97

In other patients with acute motor GBS, distal CMAPs and conduction block in forearm and elbow segments have resolved without signs of temporal dispersion, albeit after 2–5 weeks, which is later than in patients in the Kuwabara et al. study; approximately half of these patients had anti-ganglioside antibodies. 96,98 This pattern was labeled acute motor conduction block neuropathy and was considered to be related to AMAN and to be due to an antibody-mediated attack on nodal gangliosides.

Excitability studies of the median nerve at the wrist in AMAN were normal, except for the recovery cycle, which showed an abrupt increase in threshold at short interstimulus intervals of 2.0–2.5 ms without an accompanying increase in refractory period, a finding not observed in sensory axons. 99,100 When, however, refractoriness was assessed by 2 supramaximal stimuli (instead of a supramaximal conditioning stimulus followed by a test stimulus tracking a 40% CMAP), the duration of the refractory period was increased. 100 Abnormal excitability indices usually reflect axonal membrane dysfunction at the stimulus site. Because the recovery cycle curves in AMAN differed from those observed in other conditions with prolonged refractory period, such as during application of depolarizing currents, ischemia, or cooling, the investigators suggested that they reflect conduction failure of the second impulse distal to the wrist; for instance, in distal axon branches, rather than Na+ channel dysfunction at the wrist. It was considered unlikely that these changes were related to axonal degeneration, because the recovery cycle was normal in other diseases with axonal degeneration. Therefore, the biophysical basis of the abnormal recovery cycle in AMAN was assumed to be Na+ channel blocking, occupation of the nodal gap by invading macrophages yielding an increased resistance for nodal currents, or paranodal myelin detachment yielding short-circuited nodal currents. 85 An argument against the first assumption is that Na+ channel blocking by tetrodotoxin yields abnormalities distinct from AMAN, including decreased refractoriness and threshold electrotonus abnormalities. 101 Furthermore, in a patient with acute motor conduction block neuropathy, excitability studies, including the refractory period, were completely normal. 102

The effects of anti-ganglioside antibodies on the neuromuscular synapse, as found in ex vivo studies, may also occur in human GBS. Single-fiber electromyography in patients with antibodies to GM1, GM2, GD1a, or GD1b showed single impulse blocking and concomitant impulse blocking of 2 muscle fibers with normal or slightly increased jitter values. These findings are consistent with dysfunction of neuromuscular synapses and axon branches. 103 Other types of electrophysiological abnormalities in GBS associated with several types of anti-ganglioside antibodies included decrement, increment, markedly increased jitter, and decreased CMAPs (reviewed by Plomp and Willsion 104). These abnormalities may reflect primary neuromuscular synapse pathology but may also be secondary to axonal degeneration.

CIDP. CIDP is characterized by progressive sensorimotor, mainly motor, or purely sensory deficits that progress over >2 months. The course is relapsing–remitting, gradually worsening, or stepwise worsening. The distribution can be diffuse or mainly distal, or may predominantly affect upper extremities.

Pathological studies of roots, plexuses, and nerves showed loss of myelinated fibers, onion
bulbs, axonal degeneration, endoneurial or subperineurial edema, and infiltrates. Teased fiber preparations showed denuded axons, thinly myelinated axons, and paranodal demyelination. Electromicroscopy of longitudinal sections of superficial fibular nerve axons showed multivesicular bodies in paranodal loops, vacuoles in Schwann cell cytoplasm, and vacuoles in axoplasm. Immunochemistry revealed that the normal staining of Nav and Kv7.2, the slow K+ channel, at the node and of contactin-associated protein-2 (Caspr-2) at the paranode could be lost and was replaced by spots or diffuse reactivity of Caspr-2, Nav, and Kv7.2 along the internodal axolemma; Caspr-2 staining was of a higher than normal intensity. These findings were considered to reflect loss of axon–Schwann cell contact. They resemble the focal expression of Nav channels observed during recovery from experimental allergic neuritis.

The pathogenesis of CIDP is poorly understood. Cellular immunity is suggested by the finding that demyelination is mediated by invasion and stripping (delamination) of myelin lamellae by T cells and macrophages. Humoral immunity is suggested by induction of demyelination in animals by IgG or sera from CIDP patients and by the finding of antibodies against P0, myelin P2 protein, PMP22, or neurofascin in a minority of patients. Myelinated nerve fibers of CIDP patients showed immunoglobulin and complement deposits, also indicating an antibody-mediated process.

Several studies suggested that genetically determined factors in the immune system and other genetic factors contribute to development of CIDP. B cells in CIDP patients exhibit impaired expression of the inhibitory Fc-gamma receptor IIB, which is critical for the balance between tolerance and autoimmunity. Apoptosis of T cells by expression of the Fas receptor on their membrane is impaired in CIDP, suggesting a defect in switching off the immune response; the impairment is more pronounced in patients with a progressive course and axonal damage on needle electromyography. In CIDP, the SH2DA gene has a low number of GA repeats that may result in defective elimination of activated T cells. Single-nucleotide polymorphisms affecting the N-terminal fragment of the paranodal adhesion molecule transient axonal glycoprotein-1 (TAG-1) are associated with unresponsiveness to intravenous immunoglobulins (IVIg). Because TAG-1 is essential for proper location of juxtaparanodal K+ channels, and because axonal dysfunction contributes to IVIg unresponsiveness, it has been suggested that TAG-1 mutations may unfavorably alter K+ channel distribution so that axons are less well protected against the effects of demyelination. In nerve biopsies of CIDP patients, several genes related to pain mediation, immunity, inflammation, and remyelination are up- or downregulated. In turn, inflammation may induce expression of other subtypes of voltage-gated Na+ channel subtypes in dorsal root ganglia that are normally expressed. These alternative subtypes may induce abnormal firing patterns and result in pain sensations.

Excitability studies of the median nerve at the wrist in CIDP patients have shown increased thresholds in stimulus–response curves. Other excitability indices were also altered, but were not consistent between studies. This variability may be related to differences in disease characteristics, as threshold electrotonus abnormalities were greater in patients with severe disability, long disease duration, and marked slowing on NCS. The abnormality consisted of increased threshold change in hyperpolarizing threshold electrotonus of which the mechanism is unknown. In 2 studies, SDTC was decreased and rheobase increased, which is consistent with increased thresholds to nerve stimulation. The decreased SDTC was, however, unexpected, because exposure of additional axon membrane by paranodal demyelination would have increased nodal capacitance and, therefore, would have increased the passive component of SDTC. This may reflect a decrease in persistent Na+ current density due to nodal enlargement or short-circuiting of applied current by inflammatory edema.

Excitability tests of motor axons at the wrist were compared before and after IVIg treatment for CIDP. Immediately after IVIg infusion the following changes were noted: stimulus–response curve thresholds decreased; SDTC shortened; accommodation during depolarizing threshold electrotonus increased; and absolute super- and subexcitability values decreased. During the weeks thereafter, these indices slowly reverted to preinfusion values. Because the changes occurred too rapidly to be explained by remyelination or axonal regeneration, they may indicate that IVIg normalized axon membrane function by an unknown effect on ion channels and pumps. After an average of 15 months of IVIg courses, excitability indices approached normal values and weakness decreased. The excitability changes after IVIg suggest that motor axons were hyperpolarized prior to treatment and that IVIg shifted resting membrane potential toward more depolarized values. Only the short-term decrease in SDTC cannot be explained by a depolarizing shift in resting membrane potential, because this should have increased SDTC. The hyperpolarization before
IVlg treatment may have been caused by remyelination with short internodes, because shorter internodal distance implies greater numbers of nodes, Na\(^+\) channels, Na\(^+\) influx, and, consequently, more electrogenic Na\(^+\)/K\(^+\) pump activity.\(^{123}\)

To determine whether conduction block can be precipitated by changing resting membrane potential in axons with reduced safety factor due to demyelination, excitability studies were performed in CIDP patients during ischemia induced by cuff inflation and in the post-ischemic period.\(^{124}\) In CIDP, CMAPs decreased during and after ischemia. Because this was not observed in normal subjects, it was attributed to conduction block. Ischemia gives rise to Na\(^+\)/K\(^+\) pump failure, loss of ionic concentration gradients, depolarization, and Na\(^+\) channel inactivation.\(^{125}\) The latter decreases the safety factor, because fewer Na\(^+\) channels are available for impulse generation. Release of ischemia increases Na\(^+\)/K\(^+\) pump activity, because the ionic imbalance drives the pump to restore ionic concentration gradients. Because the pump is electrogenic, hyperpolarization ensues. Hyperpolarization also reduces the safety factor, because more driving current is needed to overcome the large potential difference and generate sufficient nodal depolarization for impulse generation. In normal subjects, the safety factor is sufficiently large to ensure impulse transmission despite these changes in resting membrane potential. In CIDP, however, the safety factor is already reduced due to demyelination, and the additional reduction due to de- or hyperpolarization will induce conduction block.

**MMN.** MMN is characterized by asymmetric lower motor neuron weakness, often more prominent in upper than in lower limbs. Patients may suffer from cold paresis, heat paresis, or both (see above). In typical cases, motor NCS reveal conduction block, marked slowing, or both, whereas sensory conduction in the same nerve segment is normal.\(^{126}\) It remains unclear whether motor conduction block and slowing represent paranodal demyelination, segmental demyelination, changes in resting membrane potential, or ion channel dysfunction at the node of Ranvier (Fig. 1).\(^{127}\)

Pathological studies of nerves containing motor axons were performed on biopsy specimens taken from forearm nerves, the brachial plexus, or the obturator nerve.\(^{62,128–130}\) Transverse sections showed thinly myelinated axons and small onion bulbs, consistent with demyelination and remyelination, as well as loss of myelinated axons and regenerative clusters, consistent with axonal degeneration and regeneration.\(^{128,129}\) In 1 study, transverse sections and teased fiber preparations showed virtually no demyelination and only axonal degeneration, suggesting that the primary pathology in MMN affects axons rather than the myelin sheath. In 2 patients, small perivascular lymphocyte infiltrates were seen, possibly reflecting an inflammatory process.\(^{62}\)

IgM anti-antibodies against GM1 were found in 20–80% of patients with MMN, but they were also found in patients with other disorders, including motor neuron disease.\(^{131}\) Nevertheless, anti-GM1 antibodies may play a role in the pathogenesis of MMN because: (i) high-titer antibodies are specific for MMN; (ii) patients with antibodies have more weakness and evidence of axon loss on NCS than patients without antibodies; and (iii) most anti-GM1 containing sera of MMN patients activate the classical complement pathway.\(^{132,133}\) Serum IgM from patients with MMN bound more strongly to a lipid mixture containing GM1, galactocerebroside, and cholesterol than to GM1 alone, indicating that the lipid environment of GM1 influences its binding to IgM.\(^{134}\) However, anti-GM1 antibodies cannot be detected in approximately 40% of MMN patients, so other antigens may be targeted in these patients.\(^{132}\) The IgM of some MMN patients reacted to disulfated heparin disaccharide, but the significance of this finding is unclear, as it is unknown where this substance is present on nerve fibers.\(^{131}\)

In patients with MMN, focal polarizing currents were applied at the site of conduction block, and the effect on the CMAP evoked proximal to the block was measured.\(^{58}\) In 2 nerves, the CMAP increased during application of a hyperpolarizing current. This was considered to be consistent with the disappearance of block in axons that were depolarized prior to application of the polarizing currents. In 3 other nerves the CMAP increased after application of a depolarizing current, suggesting that the block was caused by focal hyperpolarization of axons. In 1 nerve, the proximally evoked CMAP decreased during depolarizing as well as during hyperpolarizing currents, suggesting that depolarized axons and hyperpolarized axons may coexist within a nerve. The latter finding illustrates the potential weakness of compound action potential recordings; if the axons within a nerve are affected by different disease mechanisms, the net result may be no change at all, or an average change from which it is impossible to derive the pathophysiological events.

Excitability studies in MMN patients that have been performed distal to sites with motor conduction block have shown fanning-out of threshold electrotonus, decreased /V slope, decreased refractoriness, and increased superexcitability.\(^{135}\) The
abnormalities resemble those encountered during application of hyperpolarizing current to a nerve and suggest that some axons in MMN are hyperpolarized. This was supported by the return to normal of variables dependent on Na\(^+\) channel function and variables dependent on K\(^+\) channel function during application of a depolarizing DC current at the site of stimulation. To explain the focal hyperpolarization, the following was hypothesized: At the site of the lesion with conduction block, Na\(^+\)/K\(^+\) pump activity is blocked due to edema or antibodies; this causes permanent depolarization, which, in turn, yields continuous Na\(^+\) influx through persistent Na\(^+\) channels; the accumulated Na\(^+\) ions are removed at adjacent healthy parts of the axon by increased activity of the electronegative Na\(^+\)/K\(^+\) pump, yielding hyperpolarization distal to the lesion. Excitability tests in unaffected nerves of MMN patients were essentially normal, indicating that axonal membrane dysfunction is not generalized in MMN. Another study indicated decreased SDTC outside of sites with conduction block, but the excitability protocol was limited and did not involve threshold tracking. After IVIg treatment, SDTC decreased and rheobase increased within 3–5 days, which is too early to be explained by remyelination or axonal regeneration. The investigators suggested that the decrease in SDTC reflected a decrease in persistent Na\(^+\) current. Such an effect of IVIg may be beneficial for axonal survival, because it limits intraxonal Na\(^+\) accumulation. Excessive Na\(^+\) accumulation may induce reversal of the Na\(^+\)/Ca\(^{2+}\) exchanger, resulting in Na\(^+\) being extruded from the axon in exchange for Ca\(^{2+}\), increase in intraxonal Ca\(^{2+}\) concentration from nanomolar to micromolar values, and Ca\(^{2+}\)-mediated axonal degeneration. Because, however, not all excitability variables were investigated, the decrease in SDTC may also have been secondary to a change in membrane potential.

Anti-MAG Neuropathy. Anti-MAG neuropathy is associated with IgM antibodies against MAG. It is characterized by slowly progressing symmetrical sensorimotor deficits and sometimes severe sensory ataxia. The IgM is likely to be the pathogenic factor, because the antibodies are directed against

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**FIGURE 2.** Myelin-associated glycoprotein (MAG) function and axon diameter. Left: normal axon; by means of Schwann cell–axon signaling, MAG induces neurofilament sidearm phosphorylation; the negatively charged phosphate groups repel each other, ensuring neurofilament spacing and maintenance of axon diameter. Right: anti-MAG neuropathy; MAG function is impaired by anti-MAG antibodies; neurofilament sidearms are dephosphorylated, resulting in neurofilament clustering and failure to maintain axon diameter.
MAG, and passive transfer of human IgM anti-MAG antibodies to chickens produces a neuropathy with the same pathological features as in humans, including demyelination, widening between myelin lamellae, and IgM deposits. A drug treatment with convincing efficacy is not available.

The transmembrane glycoprotein MAG is located in non-compact myelin, including paranodal loops, the area apposing the axon, and alongside Schmidt–Lanterman incisures. MAG consists of 5 extracellular immunoglobulin-like domains to which sugar residues are attached, a single transmembrane segment, and a cytoplasmic tail. The sugar residues form the HNK-1 epitope, which is the antigen for anti-MAG antibodies and which is also expressed by P0, PMP22, and sulfated glycolipids (reviewed by Quarles and Weiss and Latov and Renaud). MAG has 4 known actions. First, it ensures adhesion and spacing of non-compact myelin lamellae by homologous adhesion between extracellular MAG residues of adjacent Schwann cell membranes. Second, it maintains axon diameter by promoting attachment of negatively charged phosphate groups to the side arms of medium and heavy axonal neurofilaments. The repelling forces between the phosphate groups induce spacing between neurofilament sidearms so that axon diameter is maintained (Fig. 2). Consistent with this function, local axon diameter increases with the amount of MAG expression, and MAG-null mice demonstrate demyelination and small axon caliber. The axolemmal receptors that interact with MAG possibly include Nogo, neurotrophins, glycoproteins, and gangliosides (reviewed by Steck et al.). Third, MAG protects the axon against degeneration induced by toxic substances, possibly through signaling between the extracellular MAG component and axolemmal gangliosides. Fourth, in the mature central nervous system, it inhibits elongation of axonal growth cones during regeneration by signaling to receptors on the axolemma. Potentially, anti-MAG antibodies may impair any of these actions.

Pathological studies of distal sensory lower limb nerves have shown IgM deposits in the myelin sheath, demyelination, axon loss, and widening between myelin lamellae. The myelin widening increased with the depth of IgM penetration, suggesting that the antibodies cause loss of the role of MAG in adhesion between lamellae. The IgM deposits are found in non-compact myelin where...
MAG is localized, but also in compact myelin, indicating that the IgM is not only directed to MAG but also to other molecules that bear the HNK-1 epitope. Terminal complement was found near blood vessels but not in the myelin, suggesting that complement may be involved in the initial injury of the Schwann cell basement membrane, but not in demyelination. Sural nerve biopsies revealed a decreased nearest neighbor distance between axonal neurofilaments, consistent with impairment of the role of MAG in maintaining neurofilament phosphorylation. In earlier studies, it was hypothesized that the primary pathology in anti-MAG neuropathy is axonal and, given the role of MAG in Schwann cell to axon signaling, this cannot be ruled out. In 1 patient, autopsy showed generalized IgM deposits in roots and peripheral nerves, but axon loss was limited to the sciatic nerve and demyelination to the sural nerve. These findings were suggested to reflect a sequence found after axotomy in cats. This consisted of primary distal axon atrophy, followed by secondary myelin wrinkling, nodal lengthening, and internodal demyelination. The axotomy model was, however, based on acute injury, and it is uncertain whether it can be applied to a chronic disorder like anti-MAG neuropathy.

NCS in typical cases show prolonged DMLs consistent with demyelination, less pronounced slowing in adjacent forearm and lower leg segments, and decreased CMAPs and sensory nerve action potentials in lower limbs, consistent with axon loss. This pattern is considered unique for anti-MAG neuropathy, as it does not occur in other demyelinating neuropathies such as CIDP and MMN and not in axonal neuropathies such as diabetic neuropathy, where DMLs are not consistent with demyelination. Standardized motor and sensory NCS in nerves with short, medium-length, and long axons, revealed that DMLs were more prolonged, and signs of axon loss were more prominent in nerves with longer axons (Fig. 3). The combination of length dependence of both axon loss and distal demyelination was not present in disease controls with CIDP and normal controls.

Length dependence, however, is known to be a feature of axonal polyneuropathies, where it can be explained by the vulnerability of longer axons to a generalized disease process. Length dependence of features consistent with demyelination is not well understood, and several mechanisms have been proposed. In patients with anti-MAG neuropathy, skin biopsies reveal IgM deposits in small myelinated axons that are more prominent in biopsies taken from the distal part of extremities than in biopsies taken from the proximal part. This suggests that the distal part of nerve fibers is more vulnerable to anti-MAG antibodies, either due to a more permeable blood–nerve barrier or to more prominent MAG expression. Although it is unknown whether this also holds true for large-diameter motor and sensory axons, it may explain why distal axons are affected predominantly in anti-MAG neuropathy. Alternatively, impairment of neurofilament phosphorylation by anti-MAG antibodies may cause neurofilament accumulation, which may impair axonal transport and induce axonal degeneration that is more prominent in more distal parts of longer axons. Moreover, neurofilament clustering may also yield an increased longitudinal intra-axonal resistance. Computer simulations have shown that this resistance is one of the most important determinants for conduction velocity, so that neurofilament clustering may contribute to distal conduction slowing in patients with anti-MAG neuropathy.

**POEMS Syndrome.** The full clinical picture of POEMS syndrome comprises polyneuropathy, organomegaly, endocrinopathy, M-protein (IgG or IgA), skin changes, massive peripheral edema, pleural effusion, pulmonary hypertension, ascites, and thromboembolic events. The polyneuropathy is progressive and, in approximately 50% of patients, is the initial and only sign. One of its features is severe pain in the feet. POEMS syndrome is associated with overproduction of vascular endothelial growth factor (VEGF) by monoclonal plasma cells, which results in elevated serum VEGF levels, vascular permeability, and neovascularization. Treatment is essential and is directed at decreasing VEGF levels by chemotherapy, autologous blood stem cell transplantation, or thalidomide. Untreated patients die from multiorgan failure.

Pathological studies have shown VEGF staining in endoneurial vessels, epineurial vessels, and Schwann cells; endoneurial edema; loss of small myelinated axons with preserved unmyelinated axons; segmental demyelination; widened nodal areas; loosening of inner and outer myelin lamellae; and decreased number of neurofilaments. The loss of small myelinated axons correlates with the presence of pain, suggesting loss of inhibitory functions that are normally mediated by myelinated axons.

NCS show slowing consistent with demyelination in forearm and upper arm segments and signs of axon loss in lower limb nerves; DMLs are less prominently slowed, and conduction block is rare. Taken together, the pathological and electrophysiological findings suggest that POEMS syndrome affects predominantly intermediate nerve segments and nerve trunks by VEGF-mediated...
breakdown of the blood–nerve barrier. This is in contrast to some other immune-mediated neuropathies in which antibodies gain access to the most distal and most proximal parts of axons that are less well protected by the blood–nerve barrier.

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