Inflammatory Neuropathies

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ABSTRACT

Inflammatory neuropathies are acquired disorders of peripheral nerves and occasionally of the central nervous system that can affect individuals at any age. The course can be monophasic, relapsing, or progressive. Inflammatory neuropathies are classified as acute or chronic. The acute form reaches a nadir by 4 weeks and the chronic form over 8 weeks or greater. The most common example of an acute inflammatory neuropathy is acute inflammatory demyelinating polyradiculoneuropathy (AIDP), which is part of the Guillain-Barré syndrome (GBS). The most common chronic inflammatory neuropathy is chronic inflammatory demyelinating polyradiculopathy (CIDP). Other chronic inflammatory neuropathies are multifocal motor neuropathy (MMN) and the Lewis-Sumner syndrome. The Fisher syndrome and Bickerstaff brainstem encephalitis occur acutely and have clinical overlap with AIDP.

KEYWORDS: Guillain-Barré syndrome, acute inflammatory demyelinating polyradiculoneuropathy, chronic inflammatory demyelinating polyradiculopathy, multifocal motor neuropathy, Lewis-Sumner syndrome

ACUTE INFLAMMATORY NEUROPATHIES

The Guillain-Barré (GBS) syndrome is characterized by the acute onset of progressive symmetric ascending weakness associated with areflexia. GBS has an incidence of 0.6 per 100,000.¹ The Guillain-Barré syndrome was named after two French neurologists, Georges Guillain and Jean-Alexandre Barré, who along with Andre Strohl described a pattern of acute ascending paralysis with an albuminocytological dissociation in cerebrospinal fluid (CSF).² Recently, there has been an effort to distinguish different forms of the syndrome based on time course and clinical features. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is the most common form of GBS. AIDP is a motor more than a sensory syndrome with demyelinating electrodiagnostic features. Other acute neuropathies in the Guillain-Barré syndrome include acute motor sensory axonal neuropathy (AMSAN) characterized by very rapid and severe axonal damage with slow and incomplete recovery, and acute motor axonal neuropathy (AMAN) with motor axonal features and a rapid favorable recovery. The Fisher syndrome is a triad of ophthalmoplegia, ataxia, and areflexia and may exist in isolation or as a part of AIDP.

ACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

Clinical Features

AIDP presents with ascending proximal and distal weakness. Sensory symptoms including paraesthesias and pain often either proceed or accompany weakness. Cranial nerve dysfunction can also occur. A few
patients have either isolated weakness or sensory symptoms. The lower extremities are usually affected first, but occasionally both upper and lower extremities are affected simultaneously. Rarely, the upper extremities are affected first. Weakness is usually distal greater than proximal, but both can be equally affected. Weakness often affects ambulation resulting in a dystaxic gait contributed to by a loss of proprioceptive input. Cranial nerve involvement can manifest as bilateral facial nerve dysfunction and dysphagia, which can jeopardize protection of the airway. Respiratory muscles may be affected and vigilant monitoring of respiratory parameters is required. Assisted ventilation is required in up to a third of patients. Areflexia of all four extremities occurs in the majority of individuals at some point in the illness, but a few patients will maintain reflexes. Rarely, extensor plantar responses are detected early in the course. Autonomic dysfunction resulting in cardiac dysrhythmia or blood pressure instability may be present. Up to half of patients with AIDP report severe incapacitating low back pain.

Preceding infections and vaccinations have been associated with AIDP. Serologic evidence for infection with Campylobacter jejuni (C. jejuni), cytomegalovirus, and Epstein–Barr virus infection have been detected in AIDP patients. A greater incidence of AIDP was seen among individuals who were administered the swine influenza vaccine in 1976, but influenza vaccine administered since has failed to show this association. However, the Centers for Disease Control recommend caution when vaccinating patients with a history of AIDP within 6 weeks of a previous vaccination.

Pathogenesis

Although the mechanism of AIDP is unknown, it is believed that inflammatory cells target specific epitopes on myelin. Exposure to a virus that appears similar to myelin may prime the immune system to attack myelin. Molecular mimicry is believed to occur where the immune system recognizes the myelin epitope as “foreign” and targets it for destruction. An autopsy study demonstrated activation of complement-coating myelin and subsequent vesicular disruption of the myelin.

The inflammatory process in AIDP is multifocal resulting in segmental demyelination at sites along multiple nerve roots and peripheral nerves, accounting for the term “polyradiculoneuropathy.” Secondary axonal loss occurs to varying degrees because the inflammatory process affecting myelin is in close proximity to axons causing “innocent bystander” damage. Pathologic features of demyelination include myelin ovoids filled with myelin debris, which are subsequently removed by macrophages. Remyelination subsequently takes place by Schwann cell duplication. Following remyelination, myelinated segments are often shorter with variable internode lengths, resulting in mildly slower conduction ability that may be permanent.

Diagnosis

Electrodiagnostic studies, especially nerve conduction studies (NCSs), are an important component in the diagnosis of AIDP. There are continuing efforts to design sets of electrophysiologic criteria to diagnose AIDP. Most are modifications of those proposed originally by Albers and Kelly. Summary data from NCS studies over the first 50 weeks of AIDP show that 85% of patients fulfill demyelinating criteria in motor nerves by week 3, but fewer meet criteria early on in the illness. A retrospective analysis of the diagnostic criteria for AIDP concluded that a conduction velocity of <70% of the lower limit of normal and a distal latency of >150% of the upper limit of normal was highly sensitive and had a specificity of nearly 100% for AIDP. NCSs should include at least three motor nerves with proximal and distal stimulation, F-waves or H-waves, and sensory nerves. Prolonged F-waves or absent H-waves are often the first abnormality noted and occurs within days in some AIDP patients. Distal latencies may be slightly prolonged and conduction velocities mildly slowed. Sensory nerves may show a predilection for very distal involvement, which because of the relative positions of digital and sural recording electrodes, results in abnormal responses in the upper extremities often before the lower extremities resulting in “sural sparing.” This pattern is atypical for a length-dependent polyneuropathy and can help distinguish AIDP from other neuropathies. Conduction block and abnormal temporal dispersion are hallmarks of acquired demyelination and are more likely to be encountered as the illness progresses. Needle electromyography can show decreased recruitment initially, followed by fibrillation potentials over weeks 2 to 5 in proximal and distal muscles simultaneously.

As the course of AIDP evolves, more electrodiagnostic diagnostic criteria are met. Initially, F-waves may not be significantly prolonged and may not fulfill criteria for demyelination. However, over time the majority of patients have absent or prolonged F or H responses. Motor nerve abnormalities peak by 3 to 4 weeks. The degree of conduction block is felt to directly correlate with clinical improvement. The amplitude of the responses increases as the conduction block is repaired. This change can occur rapidly over the following weeks, but in some patients is prolonged. The best electrodiagnostic indicator for a rapid or good recovery is maintained motor amplitude, which can be calculated as a percentage of the lower limit of normal. Patients who have an average amplitude >10% of the lower limit of normal likely have a major component of conduction block which has the potential to reverse.
Conversely, amplitudes < 10% during illness are seen in patients with a greater degree of axonal injury and a more prolonged recovery.

CSF analysis aids in confirming the diagnosis of AIDP. CSF examination typically shows an albuminocytologic dissociation defined as an elevation of the protein or albumin concentration without an elevated white blood cell count. This finding occurs in 80% of individuals with AIDP and is more likely to be detected after the second week of the illness. CSF pleocytosis can occur, but a significant pleocytosis of greater than 30 cells/mm³ is reported in only 1 to 2% of cases.

Imaging evaluation of the spine is useful to exclude structural causes of paraplegia or quadriplegia. Magnetic resonance imaging (MRI) may show enhancement of the lumbar sacral nerve roots or cranial nerves in AIDP. A prospective analysis of 24 AIDP patients found enhancement with gadolinium of the cauda equina in 83% of patients imaged within the first 2 weeks of symptoms. Patients with severe weakness were more likely to have enhancement.

Prognosis

There are several factors that influence the prognosis in AIDP. Older age, rapidly progressive course of illness, marked axonal loss, and severe illness requiring mechanical ventilation are associated with a worse outcome. Most patients with AIDP reach their maximum deficit within 4 weeks followed by a slow gradual recovery. One study reported that about one third of patients with AIDP questioned one year after their acute illness reported significant residual symptoms, and 22% of those patients never returned to work.

ACUTE MOTOR SENSORY AXONAL NEUROPATHY

Clinical Features

Although AIDP is the most common subtype of GBS in Northern America and Europe, the axonal form (AMSAN) of GBS is more common in Asia and South America. AMSAN is a severe axonal form of GBS with a poor outcome. AMSAN has a rapid progression to flaccid areflexic quadriplegia and ventilator dependence over a short period (~7 days). Feasby et al reported a series of four patients with “inexcitable nerves” on electrodiagnostic testing. A second series of four patients from China described by Griffin and coworkers confirmed the clinical findings described by Feasby et al. Autopsy data from these patients showed axonal degeneration without significant demyelination. However, most patients with AIDP also have some degree of axonal involvement, but AMSAN is unique because of its fulminant presentation within days leading to inexcitable nerves.

Diagnosis

NCSs in AMSAN patients are characterized by profoundly low motor amplitudes or no response, but responses with severely low amplitudes have relatively preserved conduction velocities. Sensory nerve responses are usually absent. Electromyography shows profuse fibrillation potentials consistent with an axonal process. Elevated CSF protein concentration is observed.

Prognosis

Patients with AMSAN have a severe and protracted course. Prognosis is poor, including a high mortality rate. Survivors often have significant muscle atrophy and residual weakness.

ACUTE MOTOR AXONAL NEUROPATHY

Clinical Features

AMAN is a unique disorder of motor nerves and differs from AMSAN because it spares sensory nerves and recovery is faster and more favorable. Patients become profoundly weak and frequently require respiratory support. Initial recovery can be rapid and final recovery good. One hypothesis is that AMAN and AMSAN are in the same spectrum of disorders, but AMAN is less severe. Another difference pathologically is AMSAN involves both the ventral and dorsal roots whereas AMAN involves only the ventral roots.

Diagnosis

NCSs in AMAN patients are characterized by profoundly low motor amplitudes or no response, and sensory nerve responses are unaffected. Electromyography shows profuse fibrillation potentials consistent with an axonal process.

Pathogenesis

A humoral immune response appears to have an important role in the development of AMSAN and AMAN. Both may be triggered by the same antigen and both have similar pathologic features. A prominent feature is macrophage infiltration into the periaxonal space of myelinated fibers leaving the myelin intact. Macrophages are not seen entering the myelin and myelin debris are not observed as in AIDP. AMAN may involve
temporary conduction delay without the axonal destruction seen in AMSAN because of antibody binding. Both are associated with antibodies directed at gangliosides GM1, GM1b, and GD1α; however, AMAN is also associated with GalNac-GD1α antibodies. These glycolipids and proteins may function as disease-causing specific antigens. There is evidence that *C. jejuni* infection can prime the immune system to attack the peripheral nerves. *C. jejuni* infection triggers the production of antibodies to lipo-oligosaccharides in the bacterial wall that are similar to gangliosides on myelin cells and peripheral nerves resulting in all forms of GBS. AMSAN and AMAN are most often associated with high titers signifying a recent *C. jejuni* infection.

**FISHER SYNDROME**

**Clinical Features**

Fisher first described a triad of ophthalmoplegia, ataxia, and areflexia in 1956. The classic Fisher syndrome is a relatively benign condition compared with other forms of GBS. The most common presenting symptoms are diplopia and ataxia, but other symptoms include ptosis, facial weakness, and pupillary abnormalities. Facial weakness can be delayed and may occur when other symptoms are improving. Proprioceptive sensory loss also occurs. Weakness of the extremities or progressive ascending weakness is less common. An albuminocytologic dissociation in spinal fluid is common, but may not be detected early in the course. Of note, 89% of Fisher syndrome patients have elevated GQ1b antibodies. Detection of GQ1b antibodies may be more sensitive for detecting Fisher syndrome rather than abnormal spinal fluid near the onset of symptoms. Similar to other forms of GBS, patients with Fisher syndrome often have a history of a preceding respiratory or gastrointestinal infection.

Facial, bulbar, and ocular muscle weakness can also occur in AIDP making the distinction between the Fisher syndrome and the focal variants of AIDP difficult. AIDP can present with isolated cranial nerve dysfunction, such as bilateral facial muscle weakness or Bell’s palsy. Specific antibodies such as anti-GT1b gangliosides are associated with focal and generalized forms of AIDP involving cranial nerves. Anti-GT1b, anti-GT1a, and anti-GQ1b all have a similar configuration and can be seen in AIDP. There also is cross reactivity with anti-GT1a with GQ1b. However, detection of GQ1b antibodies is most common with Fisher syndrome and may help to differentiate Fisher syndrome from AIDP.

**Diagnosis**

Electrodiagnostic studies in the Fisher syndrome are often abnormal. Sensory action potential amplitudes fall, and then quickly recover. This is explained by conduction failure rather than axonal degeneration. H or F waves may also be prolonged. There are limited data on motor nerve conductions. Demyelinating features similar to AIDP have been reported, but normal motor conductions have also been reported. Albuminocytologic dissociation is present in CSF.

**Pathogenesis**

There is controversy over whether the Fisher syndrome involves the peripheral, the central nervous system, or both. The triad of symptoms including ataxia, ophthalmoplegia, and areflexia suggests involvement of the cerebellum, brainstem, and peripheral nerves. Cranial nerve involvement does occur in Fisher syndrome. GQ1b antibodies bind to gangliosides in the neuromuscular junction of cranial nerves. GQ1b antibodies also bind to the molecular layer in the cerebellum. Little evidence has been found for binding of the GQ1b antibody to peripheral motor nerve neuromuscular junction, but peripheral sensory nerve involvement can be detected with NCSs.

The Fisher syndrome is clinically similar to Bickerstaff brainstem encephalitis, which was described in 1957. Symptoms of Bickerstaff brainstem encephalitis include ophthalmoplegia, ataxia, areflexia, paralysis, and drowsiness. Impaired consciousness or alertness is the main clinical difference between Bickerstaff brainstem encephalitis and the Fisher syndrome. Brainstem signal abnormality on MRI has been documented in some patients with Bickerstaff brainstem encephalitis. Patients with Bickerstaff brainstem encephalitis can also have positive ganglioside antibodies such as GQ1b antibodies, but the frequency of positive antibodies is lower than with the Fisher syndrome. It is proposed that focal forms of AIDP, the Fisher syndrome, and Bickerstaff brainstem encephalitis may have significant overlap and may be better described as the “anti-GQ1b IgG antibody syndrome.”

**Prognosis**

There are no clearly defined diagnostic criteria for the Fisher syndrome which contributes to difficulty making a clear distinction between AIDP with cranial nerve dysfunction, Bickerstaff brainstem encephalitis, and the Fisher syndrome. However, the prognosis for the Fisher
syndrome is excellent. Ataxia and ophthalmoplegia improve first; areflexia resolves over a longer period. Most patients begin to improve over about 2 weeks, and ataxia and ophthalmoplegia resolve over 1 to 3 months. Most have total resolution of all symptoms by 6 months after onset.35

**CHRONIC INFLAMMATORY NEUROPATHIES**

**Clinical Features**

Austin first reported a relapsing steroid-responsive polyneuropathy with elevated CSF protein concentrations in 1958.36 However, documentation of the clinical features and pathology of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) were detailed by Dyck and colleagues in 1975.37 The course of CIDP can be relapsing, which is most common, progressive, or monophasic. The clinical course of CIDP is typically gradual in onset with continued progression over greater than 2 months. This differs from AIDP, which usually reaches its nadir by 4 weeks. The prevalence rate is 2 to 5 cases per 100,000.38 CIDP can occur at any age, but is most common during the fourth through sixth decade and is slightly more frequent in men.

CIDP is a motor more than a sensory polyradiculoneuropathy, frequently with elevated CSF protein concentration. CIDP is usually symmetric and involves proximal and distal muscles.39 Symptoms start insidiously and progress over 8 weeks or longer. The lower extremities are often affected first and patients report difficulty climbing stairs or getting out of a chair due to proximal weakness as well as distal weakness manifesting as catching their toes. Distal muscle atrophy is common. Sensory findings are also present, especially involving large fiber nerves relaying vibration and position sense. Neuropathic pain is uncommon. Tendon reflexes are reduced or absent. Cranial nerves are occasionally involved. Autonomic dysfunction or respiratory weakness is rare. CIDP can manifest as a sensory predominant neuronopathy known as chronic inflammatory sensory polyradiculopathy (CISP). Pure motor variants of CIDP have also been reported.

A small percentage of CIDP patients present acutely and are initially diagnosed with AIDP. However, these patients go on to have progressive symptoms beyond 2 months. Early on, it can be difficult to differentiate between acute-onset CIDP and AIDP, but sensory involvement is usually more prominent in CIDP. Other distinguishing characteristics of CIDP are a lack of autonomic dysfunction and respiratory insufficiency.40

CIDP can be associated with other medical conditions or syndromes. Multiple myeloma, paraproteinemias, and other systemic diseases occur in combination with chronic demyelinating neuropathies. It is unclear whether CIDP associated with other medical conditions or serum antibodies represents a different disorder than traditional CIDP. CIDP associated with a paraprotein or monoclonal protein may not respond as well to typical treatments for CIDP. Two examples of syndromes that should be differentiated from traditional CIDP are POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, m-protein, skin changes) which is a chronic demyelinating neuropathy associated with elevated vascular endothelial growth factor (VEGF) levels, and CANOMAD syndrome (chronic ataxic neuropathy ophthalmoplegia M-protein agglutination disialosyl antibodies).

**Diagnosis**

The diagnosis of CIDP relies heavily on the electrodiagnostic findings indicating a demyelinating process. More than a dozen sets of electrodiagnostic criteria have been proposed. The sensitivity of the criteria varies from 30 to 90% and specificity is 90 to 100%.41 The electrodiagnostic criteria focus on motor nerve conduction because sensory nerve responses are frequently absent or of low amplitude. The American Academy of Neurology (AAN) formulated a full set of criteria for research purposes that have formed the framework for subsequent sets of criteria.42 The AAN electrodiagnostic criteria (Table 1) recommend that three of the four criteria be met in two motor nerves. However, patients rarely fulfill all criteria. To fulfill criteria for CIDP, a

<table>
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<tr>
<th>Table 1 AAN Task Force Electrodiagnostic Criteria for Chronic Inflammatory Demyelinating Polyradiculoneuropathy</th>
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<td>Must have 3 of the following in motor nerves:</td>
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<tr>
<td>1. Conduction velocity in two or more nerves</td>
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<tr>
<td>a. &lt; 80% of LLN if CMAP amplitude &gt; 80% of LLN</td>
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<tr>
<td>b. &lt; 70% of LLN if CMAP amplitude &lt; 80% of LLN</td>
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<td>2. Partial conduction block in 1 or more nerves</td>
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<tr>
<td>Proximal:distal amplitude ratio &lt; 0.8 with &lt; 15% increase in CMAP negative peak duration</td>
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<td>or</td>
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<tr>
<td>Abnormal temporal with proximal:distal amplitude or area ratio &lt; 0.8 with &gt; 15% increase in CMAP negative peak duration dispersion</td>
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<td>3. Distal latency in 2 or more nerves</td>
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<tr>
<td>a. &gt; 125% of ULN if CMAP amplitude &gt; 80% of LLN</td>
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<tr>
<td>b. &gt; 150% of ULN if amplitude &lt; 80%</td>
</tr>
<tr>
<td>4. Absent or F-wave latencies in 1 or more nerves (10–15 trials)</td>
</tr>
<tr>
<td>a. &gt; 120% of ULN if amplitude &gt; 80% of LLN</td>
</tr>
<tr>
<td>b. &gt; 150% of ULN if CMAP amplitude &lt; 80% of LLN</td>
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AAN, American Academy of Neurology; LLN, amplitude and conduction velocity; CMAP, compound motor action potential; ULN, distal latency and F-wave latency.

Modified from the Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force.43
patient should not have a paraprotein or genetic cause of their neuropathy. Koski et al recently proposed a set of criteria for CIDP with a higher sensitivity and specificity than other proposed criteria (Table 2). Sensory nerve conduction results are not included in the diagnostic criteria, but sensory nerve conduction studies are usually abnormal and sural sparing is seen in CIDP as it is in AIDP.30

Laboratory studies are helpful and elevated CSF protein concentration occurs in 80% of patients with CIDP.38 CSF cell count is usually normal, but occasionally a few lymphocytes may be detected in the spinal fluid. Nerve biopsy has a limited and controversial role in the diagnosis of CIDP. Nerve biopsy may be helpful in a patient with a chronic neuropathy, with nerve conduction studies that are equivocal. The typical pathologic features of CIDP include onion bulbs and inflammatory cell infiltrates. Teased fiber preparations are most likely to show demyelinating changes, but this is a very time-consuming procedure offered at only a few institutions.

An important part of the evaluation for CIDP includes laboratory testing for a paraprotein. Serum and urine (ideally a 24-hour urine collection) for protein electrophoresis with immunofixation should be obtained. If a monoclonal protein is identified, further work-up is required, including complete blood count, serum calcium level, and renal function. If the monoclonal protein is greater than 1.5 g/dL, a skeletal x-ray survey and bone marrow biopsy are recommended to evaluate for multiple myeloma or other myeloproliferative condition.43 Other antibodies that can be seen in chronic demyelinating neuropathies include antemyelin-associated glycoprotein (anti-MAG) antibodies associated with an IgM monoclonal gammapathy and anti-GD1b. Neuropathy associated with a paraprotein, anti-MAG, or other antibodies are important to identify because they may represent a unique disorder distinct from CIDP that does not respond to the typical corticosteroid regimen used in CIDP.

### Pathogenesis
CIDP preferentially involves nerves and spinal roots. The inflammatory process is multifocal, similar to AIDP, resulting in segmental demyelination. Secondary axonal loss occurs due to the inflammatory process. The pathologic features include demyelination, remyelination with occasional onion bulb formations, and inflammatory cells infiltrating the nerve. A cellular immune response causing T cell activation and breakdown of the blood–nerve barrier occurs. A humoral immune response also occurs causing the generation of antibodies to myelin. Experimental evidence has shown that transfer of purified human IgG from a patient with CIDP causes conduction block and demyelination in a rat model.44 Serologic evidence of C. jejuni has been found in a few patients with CIDP suggesting that gangliosides may also be a target for antibodies in CIDP as in AIDP.45

### Prognosis
CIDP can have a variable course. With treatment, 29% of patients have a monophasic course, 31% relapse, and 40% continue with progression.46 Of 38 patients treated with high-dose corticosteroids, intravenous immune globulin (IVIG), or plasma exchange for 5 years, 26% had total remission and stopped treatment, 61% had partial remission and were ambulatory, and 13% remained disabled and were unable to ambulate.47 Factors associated with a favorable outcome were a subacute onset, symmetric symptoms, good initial response to oral steroids, and predominantly distal abnormal nerve conduction. Most patients with CIDP do improve, but a subset continues to have significant impairment. CIDP rarely results in death.

### Table 2 Koski Electrodiagnostic Criteria for Chronic Inflammatory Demyelinating Polyradiculoneuropathy

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Requirement</th>
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<tr>
<td>Distal latency in &gt;50% of nerves</td>
<td>A. &gt;150% of LLN if CMAP amplitude &gt;80% of LLN</td>
</tr>
<tr>
<td>Conduction velocity in &gt;50% of nerves</td>
<td>A. &lt;80% of LLN if CMAP amplitude &gt;80% of LLN</td>
</tr>
<tr>
<td>F-wave latency in &gt;50% of nerves</td>
<td>A. &gt;120% of LLN if CMAP amplitude &gt;80% of LLN</td>
</tr>
<tr>
<td></td>
<td>B. &gt;150% of LLN if CMAP amplitude &lt;80% of LLN</td>
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<td></td>
<td>3. Absent F-wave</td>
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LLN, amplitude and conduction velocity; CMAP, compound motor action potential; ULN, distal latency and F-wave latency. Modified from reference 39

### MULTIFOCAL MOTOR NEUROPATHY WITH CONDUCTION BLOCK

#### Clinical Features
Multifocal motor neuropathy with conduction block (MMN) is a disorder of motor nerves; while sensory nerves across the site of block are normal. MMN was first described in 1988 in patients who were suspected of having a benign and predominant lower motor neuron form of amyotrophic lateral sclerosis (ALS). With further investigation, NCSs surprisingly showed multifocal motor conduction block.48 These patients also had elevated GM1 ganglioside antibodies and had clinical improvement with IVIG or immunosuppression.49
MMN typically presents with weakness in a single nerve distribution with little muscle atrophy. MMN can mimic mononeuritis multiplex when multiple nerves are affected. Onset of symptoms is often gradual over years with a predilection for the upper extremities. Finger or wrist extension weakness is a common presenting abnormality. Fociations and muscle cramps may be present and have contributed to the clinical confusion between MMN and ALS. MMN typically affects middle-aged men more than women. However, MMN rarely includes upper motor neuron signs. Tendon reflexes are often reduced in MMN. Bulbar involvement does not occur in MMN, but is typically seen in ALS.

**Diagnosis**

Patients have a lower motor neuron syndrome in conjunction with conduction block on NCSs. A diagnosis of definite MMN depends on the detection of conduction block in two motor nerves not at typical sites of compression. Conduction block is commonly defined as a drop of 50% in compound motor action potential (CMAP) amplitude comparing the proximal to distal sites of stimulation. However, some criteria use an amplitude drop of > 30% for partial conduction block. Minimal abnormal temporal dispersion is seen in MMN. Other demyelinating features in motor nerves, such as prolonged distal latency, prolonged or absent F-waves and conduction velocity slowing may be seen, but are not prominent. Occasionally, evaluation of proximal segments with stimulation at the Erb point or at the root level is needed to confirm the presence of conduction block. Some experts believe the diagnosis of MMN can be made without evidence of conduction block on NCSs. Some have proposed that MMN may be diagnosed in the absence of conduction block if other criteria are met, including demyelinating features on NCSs, positive GM1 antibodies, and MRI evidence of proximal nerve involvement.

Sensory loss and sensory nerve conduction abnormalities are typically absent or mild at diagnosis of MMN. However, they may evolve over the course of the disorder. Sensory nerve action potential amplitudes may decrease with severe disease of long duration as a result of widespread axonal degeneration. Sensory abnormalities are typically seen in the same distribution as the motor nerve involvement. MMN with sensory involvement at sites of focal conduction block has been called the Lewis-Sumner syndrome. However, findings such as elevated anti-GM1 antibodies, which are relatively specific for MMN, can be helpful. Also, elevated spinal fluid protein concentration is typical of Lewis-Sumner syndrome, but not MMN, and may help in differentiating the disorders.

**Pathogenesis**

Unlike AIDP and CIDP, MMN usually has normal or only mildly elevated CSF protein concentration. High titers of IgM anti-GM1 ganglioside antibodies (> 1:400) in the serum have moderate sensitivity and are detected in 25 to 80% of cases of MMN. MMN is believed to be an antibody-mediated disease because of the presence of GM1 antibodies and response to IVIG. Nerve biopsy is rarely helpful in the diagnosis. Focal segments of nerve enlargement may be seen on ultrasound.

**Prognosis**

The disease course may be gradually progressive, step-wise, or it may stabilize. Overall, the prognosis for MMN is typically favorable, but long-term treatment with IVIG is often required. Life expectancy is typically not affected by this disorder. Corticosteroids can worsen MMN and may serve as a mechanism to aid in differentiating MMN from CIDP.

A better overall prognosis is predicted when axonal injury and muscle atrophy is limited. Low distal motor amplitude on NCS is associated with a worse prognosis. A younger age of onset and elevated GM1 titers may also be associated with a more favorable outcome. Clinical improvement with IVIG is associated with a more favorable prognosis. IVIG may lose its effectiveness over years of therapy, which can necessitate increasing doses of IVIG to prevent worsening conduction block and cumulative axonal damage. However, progression of the disease may occur despite increasing doses and frequency of IVIG.

**LEWIS-SUMNER SYNDROME**

**Clinical Features**

In 1982, Lewis and Sumner described a series of patients with a mononeuritis multiplex pattern of persistent multifocal motor conduction block, segmental demyelination, and sensory nerve involvement. This syndrome was called multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) to denote its clinical findings. It was later named Lewis-Sumner syndrome (LSS). LSS has motor conduction block similar to MMN, but unlike MMN, patients also have sensory nerve conduction block. LSS and MMN have similar clinical features, including asymmetric involvement often beginning in the upper extremities. Weakness is typically distal affecting the fingers and wrist. Sensory involvement often presents in a specific nerve distribution rather than a stocking glove distribution. Neuropathic pain can also be an initial symptom. However, weakness and sensory complaints usually present together in LSS. Reflexes are decreased or absent. Cranial
nerve involvement may also be seen in LSS and may be more common than in MMN.62

**Diagnosis**

The electrodiagnostic findings in LSS include a combination of either conduction block or partial conduction block in at least one nerve in addition to sensory nerve conduction abnormalities. Conduction block is typically found in the upper extremities most commonly in the median and ulnar nerves. Other features of demyelination including slowed conduction velocity, prolonged distal latency, and prolonged F-waves can be seen. Sensory responses, including sural nerve conductions, can be diffusely abnormal or absent.63

There are no specific laboratory data or antibodies that are useful in the diagnosis of LSS. Spinal fluid analysis often shows elevated protein concentrations. Sensory nerve biopsy can have prominent demyelinating features, including segmental demyelination, inflammatory infiltrates, and loss of large myelinated fibers.62,64

**Prognosis**

Prognosis for LSS is variable, but is worse than MMN or CIDP. LSS may respond to corticosteroids or IVIG in ~60%.62 However, a significant proportion of LSS patients have progression despite therapy. Patients may have a relapsing course, but the majority has a progressive course on therapy with spread of symptoms to other extremities.

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