Current Approaches to Common Neuromuscular Problems

Jasper R. Daube, MD
Timothy R. Dillingham, MD, MS
Mark B. Bromberg, MD, PhD
Robert A. Werner, MD, MS
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Faculty

Mark B. Bromberg, MD, PhD
Department of Neurology
University of Utah
Salt Lake City, Utah
Dr. Bromberg began his academic career in basic science research. He received his doctorate in neurophysiology from the Department of Physiology at the University of Vermont and conducted research in the somatosensory and motor systems. He attended medical school at the University of Michigan and completed his neurology training and neuromuscular-EMG fellowship there, also. He was on the faculty of the University of Michigan in 1994, when he joined the University of Utah. He is a professor in the Department of Neurology and director of the neuromuscular program, the EMG laboratory, and the Muscular Dystrophy Association clinics. His clinical interests focus on amyotrophic lateral sclerosis, myasthenia gravis, and neuropathies. His research interests are in quantitative EMG, including motor unit estimation and algorithms for automated motor unit analysis.

Jasper R. Daube, MD
Professor of Neurology
Department of Neurology
Mayo Clinic
Rochester, Minnesota
Dr. Daube attended medical school in Rochester, New York at the University of Rochester. His internship in internal medicine was completed at North Carolina Memorial Hospital in Chapel Hill, North Carolina and his residency in neurology was completed in Madison, Wisconsin at the University of Wisconsin Hospital. He completed a fellowship in clinical neurophysiology both (EMG and EEG) from the Mayo Graduate School of Medicine in Rochester, Minnesota. Dr. Daube is a long-time member of the AANEM and was president of the association when the Executive Office was created in Rochester, Minnesota. His is board certified by both the American Board of Electrodiagnostic Medicine and the American Board of Psychiatry and Neurology. His interests include EMG, amyotrophic lateral sclerosis, and neuromuscular disease.

No one involved in the planning of this CME activity had any relevant financial relationships to disclose. Authors/faculty have nothing to disclose.

Course Chair: Timothy R. Dillingham, MD, MS

The ideas and opinions expressed in this publication are solely those of the specific authors and do not necessarily represent those of the AANEM.
Dr. Dillingham is professor and chairman of the Department of Physical Medicine and Rehabilitation at the Medical College of Wisconsin, in Milwaukee, Wisconsin. Dr. Dillingham graduated from the University of Washington School of Medicine in Seattle, Washington in 1986. In 1990, he completed his residency training in physical medicine and rehabilitation at the University of Washington. Dr. Dillingham’s electrodiagnostic research assessed needle electromyography in persons with suspected radiculopathy. Health services research and epidemiology are areas of research interest for him as well. He has used Market Scan claims data to determine who provides electrodiagnostic services in the United States and differences in study outcomes by different providers in persons with diabetes.

Dr. Werner is a professor in the Department of Physical Medicine and Rehabilitation (PMR) and chief of the PMR service at the Ann Arbor Veteran’s Administration (VA) Medical Center. He also has a faculty appointment in occupational medicine within the School of Public Health and in the Center for Ergonomics within Industrial and Operations Engineering. He is a 1983 graduate of the University of Connecticut’s School of Medicine and completed his PMR residency at the University of Michigan Medical Center. He completed a research fellowship sponsored through the National Institute on Disability and Rehabilitation Research in 1991. Dr. Werner’s interests include electromyography, pain management, and industrial rehabilitation. Dr. Werner is Co-director of the Ann Arbor VA Chronic Pain Clinic. He has over 70 publications in peer-reviewed journals and has been successful in receiving grant funding from several sources including the National Institute of Health, the Center for Disease Control, the National Institute for Occupational Safety and Health, Johns Hopkins University Center for Visual Display Terminals and Health Research, and the United States Postal Service. Dr. Werner has received awards for research writing from the Association of Academic Physiatrists, the American Academy of PMR, and the American College of Occupational and Environmental Medicine. Dr. Werner is on the editorial board for *Archives of Physical Medicine and Rehabilitation*, *Muscle & Nerve*, *Journal of Occupational Rehabilitation*, and *Topics in Stroke Rehabilitation*. 
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OBJECTIVES
After attending this session, participants will (1) obtain the conceptual framework for patient history and physical examination for common neuromuscular disorders, (2) understand the strengths and limitations of the needle EMG examination in the evaluation of these disorders, and (3) understand the anatomy and physiology of peripheral nerve and muscle and the pathophysiologic changes that occur with common neuromuscular disorders.

PREREQUISITE
This course is designed as an educational opportunity for physicians.

ACCREDITATION STATEMENT
The AANEM is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education (CME) for physicians.

CME CREDIT
The AANEM designates this activity for a maximum of 3.25 AMA PRA Category 1 Credit(s).™ If purchased, the AANEM designates this activity for 2 AMA PRA Category 1 Credit(s).™ This educational event is approved as an Accredited Group Learning Activity under Section 1 of the Framework of Continuing Professional Development (CPD) options for the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada. Each physician should claim only those hours of credit he or she actually spent in the educational activity. CME for this course is available 10/09 - 10/12.
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<td>Dayton, Ohio</td>
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<tr>
<th>Name</th>
<th>City/State</th>
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<tr>
<td>Michael T. Andary, MD, MS</td>
<td>East Lansing, Michigan</td>
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INTRODUCTION

Patients with symptoms of weakness are commonly referred for a nerve conduction study (NCS) and electromyogram (EMG) to look for the one of many different peripheral neuromuscular disorders that may account for their symptoms. The identifiable etiologies are distributed among myopathies, motor neuron diseases, polyradiculoneuropathies, and neuromuscular junction disorders.

Since identifiable causes of weakness make up only 11% of patients seen in an EMG laboratory, a well-defined approach should be available when they do appear. A clinical history to define the temporal course, distribution of symptoms, previous testing, previous treatments, and treatment outcomes should be combined with a focused neurological examination. Testing cranial nerves, strength, gait, tone, reflexes, and sensation before starting the study allows a much more focused and efficient study. Among these weakness is particularly important for planning the testing.

Generalized weakness in the outpatient or inpatient settings can have very different clinical pictures and approaches to the problems. Fatigue, weakness, cramps, and myalgia are common complaints in the outpatient setting, often without definitive findings on clinical examination. Hospitalized patients usually have more prominent deficits; in the intensive care unit they may be close to quadriplegic. Thus careful assessment of the clinical weakness is needed to identify the clinical problems that must be considered.

Patients with weakness are often referred by other physicians for EMG and NCS to assess for a specific disorder of concern to them. Weakness can occur with both central and peripheral diseases that are usually readily distinguished clinically. Occasional patients with unrecognized central disorders are referred for an EMG and NCS, such as foot drop in a stroke or paraparesis with a spinal cord lesion. The electrodiagnostic (EDX) physician should therefore do a limited evaluation to assure that the process is not central in origin.

EMG and NCS are a major part of the full evaluation of a patient with each of the peripheral causes of weakness: myopathy, neuromuscular junction disorder, peripheral neuropathy, polyradiculopathy, and motor neuron disease. EMG and NCS include a wide range of different tests for these disorders that cannot all be performed on every patient. The EDX physician must select those tests that will most reliably and efficiently define the underlying disorder. While a referring physician’s concern about specific clinical entities must be given high priority in determining the tests to select, the referring physician usually does not have the expertise and experience of an EDX physician. The EDX physician should therefore perform a clinical examination to determine the tests that will be performed focusing particularly on signs of objective weakness.
CHARACTERIZATION OF OBJECTIVE CLINICAL WEAKNESS FOR PLANNING EMG AND NCS TESTING

A neurologic examination is critical to planning the EMG and NCS that would most efficiently and accurately define the underlying disorder in a patient with weakness. Basic strength testing can guide the testing by suggesting the likelihood of possible underlying diseases. Reflex and sensory testing are helpful in selected situations.

Within the group of myopathies, as well as in other neuromuscular diseases, there can be quite different clinical pictures. For example, a myopathy may be distal as well as proximal, or neuromuscular junction diseases may get weaker (myasthenia gravis) or stronger (Lambert-Eaton myasthenic syndrome) with exercise. And there may be mixtures: polyradiculopathy often occurs in association with peripheral neuropathy, and is referred to as a polyradiculoneuropathy. The occurrence of such combinations will be identified as equal likelihood of polyradiculopathy and peripheral neuropathy. None the less, there is sufficient similarity of the diseases within each of these categories to classify them separately in defining the appropriate testing.

The distribution of the weakness assists in defining the likelihood of each of the major types of peripheral neuromuscular disease. The determination of likelihood is based on the usual clinical picture of a category of disease and the frequency of its occurrence in the population.

Each of the diseases could present distribution of the weakness with any one of the distributions, but the likelihood varies with the specific type of disease. The major disease groups will be referred to with abbreviations: myopathy (Myop), neuromuscular junction (NMJ), peripheral neuropathy (PN), polyradiculopathy (PolyRad), motor neuron disease (MND). Likelihood is defined by the greater than (">") signs.

Generalized distribution – clear evidence of weakness in many areas

Diffuse = similar weakness in all limb and trunk muscles
Myop > PolyRad= PN > NMJ > MND

Proximal = predominantly in proximal, limb-girdle muscles
Myop >> PolyRad > NMJ > MND > PN

Distal = predominantly in distal limb muscles
PN = PolyRad > MND > Myop > NMJ

Cranial = predominantly in cranial muscles
MND > NMJ > Myop > PolyRad > PN

Asymmetrical = greater weakness on one side, but not focal (see below)
MND > NMJ > Myop > PolyRad > PN

Focal = specific, usually unilateral area, not just asymmetrical
Focal weakness is most commonly a mononeuropathy, limited to the distribution of individual nerves, such as carpal tunnel syndrome or ulnar neuropathy. Radiculopathies and plexopathies are also typically focal in their distribution, a single root or a component of the brachial or lumbo-sacral plexus.

Muscle – rarely, focal weakness may be due to a muscle disease

With the exception of certain rare muscle disorders, focal processes require specific approaches to EMG and NCS that will not be discussed in this manuscript.

While there are exceptions, the time course of the disease often provides clues to the specific nature of a peripheral neuromuscular disease. Acute processes suggest toxic neuropathies or myopathies; subacute onset over days to weeks is likely an inflammatory disorder such as myositis and Guillain-Barre syndrome. Transient disorders are often metabolic, while fluctuating weakness is typical of myasthenia gravis. Disorders evolving over years generally are genetic or “degenerative” such as the dystrophies and MND.

Patient examples will be used to demonstrate approaches to weakness in different clinical settings.

Case 1: 67-year-old woman with leg weakness

• 8-year history of slowly progressive, painless weakness
  • 8 years ago - trouble arising from floor
  • 4 years ago - trouble arising from chair
  • 2 years ago - falls, give way of left leg
• Denies atrophy, fasciculations, muscle pain, sensory symptoms, or any upper extremity or trunk symptoms
  • Previous EMG and NCS normal

Clinical Examination: Uses upper extremities to arise from seated position.

• -2 weakness quadriceps with mild, bilateral atrophy
• -1 to -2 weakness left>right finger flexors and wrist flexors
• Remainder of neurologic examination is normal, including reflexes and sensory examination

EMG/NCS and report- see insert

This patient demonstrates the importance of the clinical examination and the information that EDX studies can provide. Each of these should be kept in mind in performing EDX studies. An EMG report will be enhanced for the referring physician by commenting on these.

• Confirm clinical impression
• Disease type
• Disease location
• Define severity
• Identify subclinical disease
• Define course
• Identify other associated disease

TOOLS FOR TESTING PERIPHERAL NEUROMUSCULAR DISORDERS

A patient with objective weakness in one of the defined distribution listed above on clinical examination will help to determine the type and extent of testing that is needed. The following EDX tools should
be considered for testing. Their specific applications are discussed separately below.

- NCS
- Repetitive nerve stimulation
- EMG
- Single fiber EMG (SFEMG)
- Interference analysis
- Turns/amplitude

NCS

Motor NCS - Patients with weakness may demonstrate a number of abnormalities on motor NCS that assist in localizing the process along the peripheral neuraxis. A low compound muscle action potential (CMAP) can occur in any of the neuromuscular diseases, but are less common in myopathy and NMJ disorders. Slow conduction, temporal dispersion, or conduction block are signs of demyelination that suggest acute or chronic, acquired demyelinating polyradiculopathies (AIDP or CIDP) or a multifocal motor neuropathy. Repetitive stimulation with exercise often shows the decrement and/or facilitation of a defect of neuromuscular transmission.

Late responses - Prolonged F-wave latencies or R1 blink latencies are signs of the proximal slowing seen in patients with weakness due to polyradiculopathies, particularly early in the course when other abnormalities on NCS may not be evident.

Sensory NCS - Low amplitude sensory responses and/or slow conduction, especially in the sural or medial plantar nerves in patients with weakness without sensory findings, suggest the possibility of a subclinical peripheral neuropathy as might occur in diabetes, myopathies such as inclusion body myositis. However, some disorders, such as amyloidosis or sarcoidosis, may affect nerve and muscle (neuromyopathies).

Repetitive Nerve Stimulation

Repetitive nerve stimulation testing should be considered in all patients who complain of generalized weakness, as they will occasionally identify an unsuspected NMJ disorder. The extent of testing depends on the level of suspicion of a NMJ disorder; if the suspicion is high, distal and proximal nerve-muscle testing before and after exercise should be performed in the limbs with greatest weakness. A decrement is evidence of a disorder of the NMJ; repair 2–3 minutes after exercise suggests myasthenia gravis. Marked facilitation is typical of Lambert-Eaton myasthenic syndrome, especially if the CMAP amplitudes are low. Repetitive CMAP suggest congenital which requires more extensive complicated, testing that will not be reviewed here.

EMG

Testing muscle with a needle recording electrode is the single most useful study of patients with weakness. Examination of weak muscles can define the underlying pathology in most patients. A normal study makes a neuromuscular disorder an unlikely cause of weakness. Short duration, low amplitude motor unit action-potentials are typical of a myopathy. Combined with fibrillation potentials and an excess of polyphasic MUAPs, these findings suggest muscle fiber necroses and/or regeneration, which can occur in many myopathies, but especially inflammatory. Myopathies typically show an increased turns/amplitude ratio with interference pattern analysis.

Variation in the size and shape of a single MUAP with or without short duration is a sign of NMJ disease, but can also occur in neurogenic disorders with denervation and ongoing reinnervation. Unstable individual MUAPs should be sought in each patient with weakness.

More precise identification of the severity of a disorder is aided by quantitation of the duration, amplitude, and phases of 30 or more individual MUAPs. Quantitation of an interference pattern with a mixture of superimposed MUAPs can be analyzed by interference pattern analysis in which the amplitude and turns are measured at a fixed force.

Reduced MUAP recruitment with long duration, polyphasic MUAPs are evidence of a neurogenic disorder. The presence of fibrillation potentials and unstable MUAPs indicate a progressing disorder, or less likely, ongoing reinnervation. Neurogenic disorders typically show decreased turns/amplitude ratio with interference pattern analysis.

SFEMG

Specialized needle EMG recordings with a 500 Hz filter and more rapid sweep settings allow the isolated recording of individual muscle fibers. Variation in the interval between two fibers in a single MUAP (jitter) can provide very sensitive evidence of a NMJ disorder. Increased jitter with normal or mildly short duration MUAPs is the most sensitive test for NMJ disorders, and may be seen in muscles without decrement in myasthenia gravis. Increased jitter with long duration, polyphasic MUAPs is evidence of a progressing neurogenic disorder such as MND.

Case 2: 20-year-old college student 2 weeks progressive generalized weakness

Day 1  Myalgia, headache, sore throat, fever
Day 10  Student Health: penicillin for “strep throat”, persistent emesis
Day 11  Emergency Room - Urinary retention, lethargy, unsteady
Day 12  Diplopia, mild proximal weakness, brisk deep tendon reflex (DTR), bilateral Babinski
Day 13  Reduced reflexes, progressive weakness, shortness of breath (SOB), tachycardia
Day 14  Hospitalized: Head computed tomography and magnetic resonance imaging scans normal; Cerebrospinal fluid (CSF) cells and protein increased
Diagnosis – Guillain–Barré with myelopathy, polyradiculoneuropathy, and autonomic neuropathy

**Treatment Plan:** Start 5 days intravenous immunoglobulin (IVIg)

**EMG/NCS #1 and report** – see insert

**EMG/NCS #2 and report** – see insert

**EMG/NCS #3 and report** – see insert

Case 2 demonstrates the evolution of a clinical disorder in which EMG provides valuable clinical guidance for both prognosis and clinical guidance. All the EMG/NCS abnormalities found in neuromuscular diseases evolve over time. These changes should be kept in mind in interpreting findings. The typical evolution of EMG findings in a patient with weakness from an acute axonal loss is shown in Table 2.

### Table 2: Evolution of electromyography findings in an acute neurogenic disorder

<table>
<thead>
<tr>
<th></th>
<th>1 week</th>
<th>2 weeks</th>
<th>6 weeks</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fibrillation Potentials</strong></td>
<td>None</td>
<td>Some</td>
<td>Many</td>
<td>None or tiny</td>
</tr>
<tr>
<td><strong>Recruitment</strong></td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td><strong>Phases</strong></td>
<td>Normal</td>
<td>Polyphasic</td>
<td>Polyphasic</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Normal</td>
<td>(Long)</td>
<td>Long</td>
<td>Long</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>None</td>
<td>Unstable</td>
<td>Unstable</td>
<td>Complex Repetitive Discharge</td>
</tr>
</tbody>
</table>

The remainder of this review will include a brief summary of the approach to weakness in each of the major groups of neuromuscular disease followed by a detailed review of the considerations in assessing a patient for possible myopathy.

### TESTS TO CONSIDER IN A PATIENT WITH SUSPECTED MND

Evaluation of MND is complicated by the variety of initial presentations both in distribution and clinical manifestations. Amyotrophic lateral sclerosis (ALS), the most common MND, typically presents with focal signs that may be one arm, one leg, bulbar, respiratory or trunk in that order of frequency. Presentation may be with purely lower motor neuron, purely upper motor neuron, or a mixture of signs in each area. Two reliable clues to ALS are: presence of motor with no sensory findings, EMG abnormalities outside the distribution of clinical findings. ALS should be considered in every patient with focal deficit if there are no sensory findings, such patients 1) with foot drop, but no pain or sensory loss, hand weakness, but no pain or sensory loss, difficulty swallowing, but no pain or sensory loss, etc. Other signs can be helpful in suggesting specific MND. Facial fasciculations suggest Kennedy’s disease; very long standing, minimally progressive, symmetrical, predominantly proximal weakness suggests a spinal muscular atrophy. Asymmetric distribution of widespread neurogenic MUAPs with a minimum of fibrillation can be residuals of poliomyelitis.

### EMG

While EMG or NCS testing could be performed first, in a patient with suspected MND it is often more efficient to begin with EMG testing, sampling weak muscles in the weakest limb in the distributions of different nerves and roots. If the abnormalities are outside the distribution of a single nerve or root, it is most efficient to then move to muscles in another limb, e.g., anterior tibial, medial gastrocnemius and vastus medialis in the leg, or first dorsal interosseous, biceps, and triceps in the arm. If abnormality is found in two limbs, thoracic paraspinal muscles at two levels can be sampled with a goal of finding abnormalities at three levels of the neuraxis. If changes are found at only two levels, or if there is bulbar weakness, cranial innervated muscles like the trapezius, masseter, or tongue should be tested. Unstable, polyphasic MUAPs can provide evidence of denervation early in the course of the disease when fibrillations may be minimal. If necessary, diaphragm EMG should be considered.

### NCS

If changes of MND are found on EMG, NCS can be limited to the limb with greatest weakness to be sure there is not a superimposed mononeuropathy or peripheral neuropathy. A critical finding in distinguishing the changes of a mononeuropathy from MND is normal sensory potentials with low amplitude motor responses.

### TESTS TO CONSIDER IN A PATIENT WITH SUSPECTED POLYRADICULOPATHY

PolyRad are often demyelinating disorders with significant slowing of conduction or conduction block. NCS testing provides the most definitive evidence of a PolyRad. NCSs are generally performed first with particular attention to motor NCSs. NCSs in a pure axonal PolyRad will be less informative, but necessary to demonstrate the extent of axonal loss.

### NCS

Starting with the most involved limb, median, ulnar, peroneal, and tibial nerves are tested with particular attention to F-wave latencies and distal latencies. If conduction velocity is slowed at all distally, the F-wave latency should be compared with an estimated F-latency. PolyRad will typically show more slowing proximally with a longer F-wave latency than F-wave latency estimate. If proximal slowing is not clearly shown by distal nerve testing, proximal conduction is most efficiently tested with blink R1 latency. Although technically more difficult, proximal slowing can also be identified by percutaneous, needle stimulation of the nerve “root” (spinal nerve) with recording from the hypothenar, biceps, abductor hallucis, or extensor digitorum brevis muscles.

### EMG

If clear evidence of PolyRad is found on NCS, the purpose of EMG becomes to determine the extent and distribution of axonal loss...
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(fibrillation potentials). Selected weak muscles in one arm and leg, and paraspinal muscles are usually sufficient.

**TESTS TO CONSIDER IN A POSSIBLE PERIPHERAL NEUROPATHY**

Despite the wide variety of forms of PN the approaches are similar with a focus on NCS. Both the axonal and demyelinating forms are identified by similar testing. The criteria for distinguishing them should be familiar to the EDX physician, but will not be discussed in this manuscript.

**NCS**

Since the disorder is typically distal and length dependent, testing the leg on the most involved side first (or the least involved if there is severe atrophy) including peroneal/anterior tibial, if there are no responses distally. F-wave testing is important to identify combined PN and PolyRad. If both disorders are present the F-wave latency and F-wave latency estimate will be similar; if there is no PolyRad, the F-wave latency will be shorter than the estimate. It is particularly important to compare proximal and distal amplitudes and configuration. Significantly lower amplitude with proximal stimulation can identify a focal conduction block (distinct from focal slowing); an irregular spreading of the CMAP shape identifies temporal dispersion, another sign of a demyelinating process.

**EMG**

The purpose of EMG is primarily to confirm the extent and distribution of axonal loss (fibrillation potentials), and should test distal, proximal and paraspinal muscles if there are any clinical or NCS signs of proximal involvement. EMG of distal arm muscles often demonstrates axonal loss with not clinical signs, usually only long duration motor unit potentials. If no fibrillation potentials are found in standard muscles, intrinsic foot muscles (abductor hallucis and dorsal interossei) will often show abnormality.

**TESTS TO CONSIDER IN A POSSIBLE MYOPATHY WITH A FOCUS ON INFLAMMATORY MYOPATHIES**

While either EMG or NCS testing could be performed first, in a possible myography it is often more efficient to begin with EMG testing, sampling weak muscles in the weakest limb in the distributions of different nerves and roots.

The following needle EMG protocol is recommended:

- Test two or three of the weakest muscles and a less involved muscle searching for fibrillation potentials, unstable MUAPs and short duration and/or polyphasic potentials
- Examine multiple areas within a muscle since findings may be scattered, giving particular attention to superficial layers where abnormalities are often more prominent in inflammatory myopathies
- If abnormalities are not found in the limbs, test thoracic paraspinal muscles at two levels and test cranial muscles with significant weakness
- If abnormalities are found in one limb, compare at least one muscle in the other ipsilateral limb to fully define the distribution
- Quantitate MUAPs in the weakest muscles if clear abnormalities are not found

The following NCS protocol is recommended:

Test the weakest limb with motor NCS and F-waves. If weakness is particularly prominent in radial or musculocutaneous innervated muscles, test radial and/or musculocutaneous nerves for focal slowing or conduction block to exclude multifocal motor neuropathy with conduction block

If there is a history of fatigable weakness, look for NMJ disorders by testing repetitive stimulation before and after exercise in clinically weak muscles, (e.g., accessory/trapezius, musculocutaneous/biceps, axillary/deltoid, femoral/rectus femoris).

**Findings in Myopathy**

The distribution of abnormality in many myopathies, especially inflammatory is proximal and paraspinal, but often with prominent changes in the anterior tibial muscle. A few myopathies, especially fascio scapulo humeral (FSH) dystrophy and DM2 myotonic dystrophy may have different findings in muscles near each other or be asymmetrical. These require more sampling to identify. A limited number of myopathies have distal weakness, especially the relatively common inclusion body myositis (Table 3).

<table>
<thead>
<tr>
<th>Table 3 Myopathies with predominantly distal weakness</th>
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</thead>
<tbody>
<tr>
<td>o Inclusion body myositis - usually</td>
</tr>
<tr>
<td>o Polymyositis - infrequently</td>
</tr>
<tr>
<td>o Centronuclear myopathy (dynamin 2)</td>
</tr>
<tr>
<td>o Nebulin distal myopathy</td>
</tr>
<tr>
<td>o Central core myopathy</td>
</tr>
<tr>
<td>o Myotonic dystrophy</td>
</tr>
<tr>
<td>o Distal dystrophies</td>
</tr>
<tr>
<td>o Amyloid</td>
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</tbody>
</table>

MUAPs in a myopathy become shorter in duration and lower in amplitude as muscle fibers are destroyed by the disease. The changes are typically proportional to the weakness. In severe disease MAUPs may have only a tiny potential from one remaining fiber in the MUAP. Increased MUAP turns and phases results from differential fiber conduction velocity with loss of synchrony because of fiber atrophy or small regenerating fibers. SFEMG also shows abnormalities with increased jitter due to reinnervation, and in-
creased fiber density due to fiber splitting and reinnervation. Early in the course of a myopathy, the findings may be patchy or subtle, requiring widespread and thorough sampling of muscles. Keep in mind each of the neuromuscular disorders that may show short duration MUAPs (Table 4).

**Table 4** Disorders that can result in short duration MUAPs

- Myopathy with muscle fiber destruction
- Neuromuscular junction disorders with severe block or end plate destruction
- Periodic paralysis and other membrane disorders
- Neuropathy with primarily nerve terminal damage
- Late stage, severe neurogenic disorder
- Early regeneration after a severe neurogenic process

MUAPs = motor unit action potentials

EMG is limited in its ability to distinguish between different etiologies. Although the findings reflect the underlying muscle fiber pathology and physiology, pathologic changes in different disorders may produce similar EMG changes such that the findings are not specific for individual diseases. The absence of abnormal MUAP changes in a clearly weak muscle can occur in some endocrine or metabolic myopathies, especially steroid myopathy.

Fibrillation potentials occur by a number of mechanisms, including segmental necrosis of fibers, fiber splitting, and from regenerating muscle fibers. Fibrillation potentials may be few in number and scattered. They tend to fire slowly at less than 4 Hz. Positive waveform fibrillation potentials are often seen. Muscle fiber atrophy results in very tiny MUAPs in long-standing disease. Myopathies with fibrillation potentials are listed in Table 5.

**Table 5** Myopathies with fibrillation potentials

- All inflammatory myopathies
- Inclusion body myositis - often with a mixture of short and long duration motor unit action potentials
- Critical illness myopathy
- Congenital myopathies - centronuclear, nemaline, congenital fiber-type disproportion
- Muscular dystrophies - dystrophinopathies, fascio scalpopum humeral, myotonic dystrophy DM1 and DM2, some limb-girdle muscular dystrophy (LGMD), most distal dystrophies
- Toxic: acute alcoholic myopathy, lipid lowering drugs
- Metabolic: acid maltase, other glycogen storage diseases after an attack, hyperkalemic periodic paralysis, paramyotonia, K-sensitive myotonia
- Rhabdomyolysis - may be quite prominent
- Muscle trauma – including previous surgery and injections

The common occurrence of fibrillation potentials in an inflammatory myopathy and the much greater incidence of inflammatory myopathy than other myopathies, make inflammatory myopathy far more likely in a patient with weakness, short duration MUAPs and fibrillation potentials. There are differences in density of fibrillation potentials among the myopathies as shown in Table 6.

**Table 6** Major Categories of Inflammatory Myopathies Listed by Density of Fibrillation

<table>
<thead>
<tr>
<th>Polymyositis</th>
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<tbody>
<tr>
<td>Dermatomyositis</td>
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<tr>
<td>Inclusion body myositis</td>
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<tr>
<td>Overlap syndromes</td>
</tr>
<tr>
<td>Connective tissue diseases sometimes with neuropathy</td>
</tr>
<tr>
<td>Scleroderma</td>
</tr>
<tr>
<td>Sjogrens</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Rheumatoid</td>
</tr>
<tr>
<td>Penicillamine</td>
</tr>
<tr>
<td>Amyloid</td>
</tr>
<tr>
<td>Bacterial myositis – Clostridia, tuberculosis, Lyme, syphilis, Whipple’s disease</td>
</tr>
<tr>
<td>Viral myositis – human immune deficiency virus, Coxackie, influenza</td>
</tr>
<tr>
<td>Parasitic myositis – trichinosis, toxoplasmosis, cysterocysis, echinococcus</td>
</tr>
<tr>
<td>Sarcoid myopathy</td>
</tr>
<tr>
<td>Eosinophilia-myalgia syndrome</td>
</tr>
<tr>
<td>Focal myositis</td>
</tr>
<tr>
<td>Vasculitis</td>
</tr>
</tbody>
</table>

Other discharges have varying significance. Complex repetitive discharges indicate long duration of disease, but do not suggest a specific type. A limited number of myotonic discharges can be seen in many myopathies and in long-standing neurogenic processes. If they are more prominent, specific diseases listed in Table 7 should be considered.

**Table 7** Myopathies with myotonic discharges

- Myotonic dystrophy, both DM1 and DM2
- Paramyotonia congenita
- Myotonia congenita
- Hyperkalemic periodic paralysis
- Potassium sensitive myotonia
- Centronuclear myopathy
- Hypothyroid myopathy
- Statin-associated myopathy
- Acid maltase deficiency
- Amyloid

The two forms of myotonic dystrophies, DM1 and DM2 differ clinically with myalgia and asymmetry in DM2. Differences in response to repetitive stimulation and the character of the myotonic discharges allow them to be distinguished from each other and more important from an inflammatory myopathy.

A number of reports have shown that the distribution of myotonic discharges in DM2 is more prominent and may be limited to proximal in the legs. It is therefore important to look there. In addition while both DM1 and DM2 have myotonic discharges in DM2 they generally wane rather than wax and wane. The end of slow-waning discharges in DM2 has characteristics that are similar to fibrillation potentials. The limited distribution of DM2 and the difference in...
pattern can result in a patient having what appears to be fibrillation potentials with short duration MUAPs, like an inflammatory myopathy. A more extensive search for myotonic discharges is needed in some patients with myalgia and minimal weakness who might have DM2.

The abnormalities in inflammatory myopathy evolve over time. Early on the findings are patchy or subtle, requiring thoroughness and widespread sampling for the short MUAPs and fibrillation potentials. The MUAPs become more polyphasic with disease progression to where they have some features of a chronic neurogenic process, including reduced recruitment and long-duration MUAPs. In chronic stages, MUAPs become more polyphasic with satellite potentials with mixed short-and long-duration MUAPs. Mild NCS changes may appear. A long standing inflammatory myopathy cannot be readily distinguished from inclusion body myositis, whose apparent incidence is increasing as specific biopsy staining for the disorder has become more prominent.

Before concluding that a patient’s clinical and EMG/NCS findings are due to an inflammatory myopathy, attempts should be made to assure that other mimic disorders are excluded (Table 8).

TABLE 8 Disorders to rule out In a suspected inflammatory myopathy

<table>
<thead>
<tr>
<th>Other Myopathies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme deficiencies</td>
<td></td>
</tr>
<tr>
<td>Congenital myopathies</td>
<td></td>
</tr>
<tr>
<td>Necrotizing myopathies</td>
<td></td>
</tr>
<tr>
<td>Toxins and drugs</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
</tr>
<tr>
<td>Ischemia</td>
<td></td>
</tr>
<tr>
<td>Heat</td>
<td></td>
</tr>
<tr>
<td>Injections</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td></td>
</tr>
<tr>
<td>Paraneoplastic</td>
<td></td>
</tr>
<tr>
<td>Other neuromuscular disease</td>
<td></td>
</tr>
<tr>
<td>Neuromuscular junction disorders</td>
<td></td>
</tr>
<tr>
<td>Polyradiculopathy</td>
<td></td>
</tr>
<tr>
<td>Spinal muscular atrophy</td>
<td></td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td></td>
</tr>
</tbody>
</table>

NCSs in myopathies are usually normal, or show only low amplitude responses if the weakness is sufficiently severe, but others should be considered as well (Table 9).

<table>
<thead>
<tr>
<th>Table 9 Myopathies more likely to have low compound muscle action potentials amplitudes on nerve conduction studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory</td>
</tr>
<tr>
<td>o Inclusion body myositis</td>
</tr>
<tr>
<td>o Severe polymyositis</td>
</tr>
<tr>
<td>Dystrophies</td>
</tr>
<tr>
<td>o Distal muscular dystrophies</td>
</tr>
<tr>
<td>o Distal myopathies</td>
</tr>
<tr>
<td>o Myotonic dystrophy</td>
</tr>
<tr>
<td>o Facioscapulohumeral dystrophy</td>
</tr>
<tr>
<td>o Emery-Dreifuss muscular dystrophy</td>
</tr>
<tr>
<td>Enzyme deficiencies</td>
</tr>
<tr>
<td>o Debrancher enzyme deficiency</td>
</tr>
<tr>
<td>o Acid maltase deficiency</td>
</tr>
<tr>
<td>Other myopathies</td>
</tr>
<tr>
<td>o Congenital myopathy</td>
</tr>
<tr>
<td>o Nemaline myopathy</td>
</tr>
<tr>
<td>o Central core myopathy</td>
</tr>
<tr>
<td>o Centronuclear myopathy</td>
</tr>
<tr>
<td>o Myofibrillary myopathy</td>
</tr>
</tbody>
</table>

Slow motor conduction or sensory NCS abnormalities suggest the additional presence of a neuropathy. While long-duration MUAPs can occur with chronic myopathies, neuromyopathies are disorders that involve both nerve and muscle directly, and must be considered when these combinations are found. They occur most commonly in connective tissue diseases, but do occur in other myopathies, particularly drugs or toxins as listed in Table 10.

<table>
<thead>
<tr>
<th>Table 10 Neuromyopathies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connective tissue disorders</td>
</tr>
<tr>
<td>Systenic lupus Erythematous</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
</tr>
<tr>
<td>Sjogrens</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
</tr>
<tr>
<td>Congenital myopathies</td>
</tr>
<tr>
<td>Myofibrillary (desmin)</td>
</tr>
<tr>
<td>Mitochondrial disorders</td>
</tr>
<tr>
<td>Metabolic myopathies</td>
</tr>
<tr>
<td>Acid maltase deficiency</td>
</tr>
<tr>
<td>Debrancher enzyme deficiency</td>
</tr>
<tr>
<td>Mitochondrial disorders</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Cyclosporin</td>
</tr>
<tr>
<td>Vincristine</td>
</tr>
<tr>
<td>Chloroquine</td>
</tr>
<tr>
<td>Colchicine</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Amyloid</td>
</tr>
</tbody>
</table>

Among the most difficult muscle problems for the EDX physician are patients with myalgia and fatigue who have no weakness or other clinical deficits. They are often classified and treated as fibromyalgia, but it must be recalled that some myopathies may have these as primary symptoms (Table 11). Some of them can be readily identified with EMG and muscle biopsy, but others will require more specific testing.
Table 11  Muscle disorders underlying myalgia and fatigue in some patients

<table>
<thead>
<tr>
<th>Endocrine</th>
<th>Hyperthyroid</th>
<th>Hypothyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic</td>
<td>Lipid storage</td>
<td>Mitochondrial</td>
</tr>
<tr>
<td>Drug – cholesterol lowering agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Polymyositis</td>
<td>Trichinosis</td>
</tr>
<tr>
<td></td>
<td>Sarcoid</td>
<td></td>
</tr>
<tr>
<td>Dystrophy</td>
<td>Myotonic dystrophy DM2</td>
<td>Becker</td>
</tr>
<tr>
<td></td>
<td>Caveolinopathy</td>
<td>Calpainopathy</td>
</tr>
</tbody>
</table>

Clinical Examples of the Application of These Principles

Case 3: 65–year-old woman with fatigue

- 2 years of difficulty with household chores, “tired”
- Difficulty squatting during exercise
- EMG 1 year ago – normal NCS and EMG
- Limited improvement on Sertaline
- Examination - mild proximal weakness; normal reflexes, cranial nerves, sensation, gait

EMG/NCS and report – see insert

Case 4: 29- year-old woman with muscle aches

- Healthy - 5 years muscle aches
- Mild elevations of creatine kinase (300 - 550)
- Examination normal
- Mild weakness, limited to left triceps
- Normal NCS

EMG/NCS and report – see insert

Case 5: 45–year-old interior designer with 3 months generalized weakness

- Diplopia brain stem astrocytoma-stable 2 yrs after radiation therapy
- Temporal lobe herpes simplex virus (HSV) encephalitis-better 1 year after Acyclovir
- Bulbar dysfunction from tumor-dexameth asme and Temazolamide
- 2 mo progressive weakness with no other symptoms or signs
- CSF and EMG performed at home - axonal and demyelinating neuropathy
- Hospital transfer - quadriparetic with deep vein thrombosis
- Normal reflexes and sensation
- MRI 10 mm mass and residuals of HSV

EMG/NCS and report – see insert

Case 6: 84-year-old woman with weakness

- Diabetes mellitus and hypothyroidism with 2 months of painless arm weakness
- Examination: Proximal symmetric arm weakness, normal reflexes
- NCS - normal

EMG/NCS and report - see insert
INTRODUCTION

Cervical and lumbosacral radiculopathies are conditions involving a pathological process affecting the spinal nerve root. Commonly, this is a herniated nucleus pulposis that anatomically compresses a nerve root within the spinal canal. Another common etiology for radiculopathy is spinal stenosis resulting from a combination of degenerative spondylosis, ligament hypertrophy, and spondylolisthesis. Inflammatory radiculitis is another pathophysiological process that can cause radiculopathy. It is important to remember, however, that other more ominous processes such as malignancy and infection can manifest the same symptoms and signs of radiculopathy as the more common causes.

This manuscript deals with the clinical approach used in an electrodiagnostic (EDX) laboratory to evaluate a person with neck pain, lumbar spine pain, or limb symptoms which are suggestive of radiculopathy. Given the large differential diagnosis for these symptoms, it is important for EDX physicians to develop a conceptual framework for evaluating these referrals with a standard focused history and physical examination and a tailored EDX approach. Accurately identifying radiculopathy by EDX whenever possible provides valuable information for treatment and minimizes other invasive and expensive diagnostic and therapeutic procedures.

SPINE AND NERVE ROOT ANATOMY: DEVIATIONS FROM THE EXPECTED

The anatomy of the bony spine, supporting ligamentous structures, and neural elements provides a unique biomechanical system that allows tremendous strength, yet flexibility. The interested reader can consult standard anatomy texts for further discussions. The important structural issues that relate to radiculopathy are addressed in this manuscript.

In the lumbar spine, the attachment and shape of the posterior longitudinal ligament predisposes the nucleus pulposis to herniation in a posterolateral direction where it is the weakest. The dorsal root ganglion (DRG) lies in the intervertebral foramen and this anatomical arrangement poses major implications for clinical EDX of radiculopathy. Intraspinal lesions can cause weakness due to their effects on the motor axons which originate in the anterior and lateral gray matter and pass through the lumbar spine as spinal roots. These roots form the “cauda equina,” or horse’s tail, the name used to describe this anatomic structure. Intraspinal lesions can also produce sensory loss by damaging the dorsal roots, which are composed of central processes from the sensory nerve cell bodies in the DRG, as they project to the spinal cord. Electrophysiologically, severe axonal damage intraspinally results in spontaneous activity on needle electromyography (EMG) and possibly reduced compound muscle action potentials (CMAPs). However, the sensory nerve action potentials (SNAPs) are preserved. This anatomical relationship provides a mechanism for further confirming whether or not a lesion is radicular (intraspinal). A destructive intramedullary (spinal cord) lesion at T11 can produce EMG findings in muscles innervated by any of the lumbosacral nerve roots and manifest the precise findings on needle EMG as those seen with a herniated nucleus pulposis at any of the lumbar disc levels. For this reason, the EDX physician cannot determine for certain the anatomic location of the lumbar intraspinal lesion producing distal muscle EMG findings in the lower limbs. EMG can only identify the root or roots that are physiologically involved, but not the precise anatomic site of pathology within the lumbar spinal canal.

In a prospective study of 100 patients with lumbosacral radiculopathy who underwent lumbar laminectomy, EMG precisely identified the involved root level 84% of the time. EMG failed to accurately identify the compressed root in 16% of patients. However, at least half of the failures were attributable to anomalies of innervation.
Another component to this study involved stimulating the nerve roots intraoperatively with simultaneous recording of muscle activity in the lower limb using surface electrodes. These investigators demonstrated variations in root innervations, such as the L5 root innervating the soleus and medial gastrocnemius in 16% of a sample of 50 patients. Most subjects demonstrated dual innervations for most muscles.68

Regarding the cervical nerve roots and the brachial plexus, there are many anatomic variations. Perneczky described an anatomic study of 40 cadavers where in all cases there were deviations from accepted cervical root and brachial plexus anatomy.47 Levin, Maggiano, and Wilbourn examined the pattern of abnormalities on EMG in 50 cases of surgically proven cervical root lesions.39 A range of needle EMG patterns was found with EMG demonstrating less specificity for the C6 root level, but more specificity and consistent patterns for C8, C7, and C5 radiculopathies. In subjects with C6 radiculopathies, half the patients showed findings similar to those with C5 radiculopathies and the other half demonstrated C7 patterns.

These findings underscore the limitations of precise localization for root lesions by EMG. The EDX physician should maintain an understanding of these anatomic variations to better convey the level of certainty with respect to diagnostic conclusions.

COMMON MUSCULOSKELETAL DISORDERS MIMICKING CERVICAL RADICULOPATHY

The symptoms of radiculopathy are nondescript and not specific for radiculopathy. Many other neurologic and musculoskeletal conditions can produce pain, weakness, and sensory symptoms. In addition to the standard peripheral neurologic examination, one of the most helpful maneuvers is to ask the patient where it hurts, then carefully palpate that area. If pain is reproduced by this palpation then the examiner should have a heightened suspicion for a musculoskeletal disorder. However, whereas a musculoskeletal disorder identified on examination makes a normal EDX study more likely, the presence of a musculoskeletal disorder does not exclude an abnormal EDX study with reliability or specificity. Common musculoskeletal disorders that produce symptoms similar to those produced by a cervical radiculopathy are shown in Table 1.

Regarding the cervical nerve roots and the brachial plexus, there are many anatomic variations. Perneczky described an anatomic study of 40 cadavers where in all cases there were deviations from accepted cervical root and brachial plexus anatomy.47 Levin, Maggiano, and Wilbourn examined the pattern of abnormalities on EMG in 50 cases of surgically proven cervical root lesions.39 A range of needle EMG patterns was found with EMG demonstrating less specificity for the C6 root level, but more specificity and consistent patterns for C8, C7, and C5 radiculopathies. In subjects with C6 radiculopathies, half the patients showed findings similar to those with C5 radiculopathies and the other half demonstrated C7 patterns.

These findings underscore the limitations of precise localization for root lesions by EMG. The EDX physician should maintain an understanding of these anatomic variations to better convey the level of certainty with respect to diagnostic conclusions.

Common entrapment neuropathies can present with symptoms similar to radiculopathy. Median neuropathy at the wrist and ulnar neuropathy at the elbow are common conditions for which patients are referred for EDX, and complicate the EDX assessment for radiculopathy. Plexopathies such as idiopathic brachial neuritis can pose diagnostic dilemmas for the EDX consultant as pain, weakness, and sensory loss are all common symptoms in both plexopathies and radiculopathies.

COMMON MUSCULOSKELETAL DISORDERS MIMICKING LUMBOSACRAL RADICULOPATHY

Conditions that present with symptoms similar to those of lumbosacral radiculopathy are shown in Table 2. In this author’s opinion, one of the most readily treatable, yet under-recognized conditions is trochanteric bursitis and illiotibial band syndrome. The illiotibial band originates at the iliac crest and has tendinous contributions from the gluteus maximus and tensor fascia latae. It runs the length of the thigh and crosses the knee joint inserting on the lateral condyle of the tibia. This band is part of the fascia lata, a layer of dense strong connective tissue enveloping the thigh.

Table 1  Musculoskeletal conditions that commonly mimic cervical radiculopathy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical symptoms/signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibromyalgia syndrome</td>
<td>Pain all over, female predominance, often sleep problems, tender to palpation in multiple areas</td>
</tr>
<tr>
<td>Polymyalgia rheumatica</td>
<td>&gt;50 years old, pain and stiffness in neck shoulders and hips, high ESR</td>
</tr>
<tr>
<td>Sternoclavicular joint arthropathy</td>
<td>Pain in anterior chest, pain with shoulder movement (adduction), pain on direct palpation</td>
</tr>
<tr>
<td>Acromioclavicular joint arthropathy</td>
<td>Pain in anterior chest, pain with shoulder movement (adduction), pain on direct palpation</td>
</tr>
<tr>
<td>Shoulder bursitis, impingement syndrome, bicipital tendonitis</td>
<td>Pain with palpation, positive impingement signs, pain in C5 distribution</td>
</tr>
<tr>
<td>Lateral epicondylitis “tennis elbow”</td>
<td>Pain in lateral forearm, pain with palpation and resisted wrist extension</td>
</tr>
<tr>
<td>De Quervain’s tenosynovitis</td>
<td>Lateral wrist and forearm pain, tender at abductor pollicis longus or extensor pollicis brevis tendons, positive Finkelstein test</td>
</tr>
<tr>
<td>Trigger finger, stenosing tenosynovitis</td>
<td>Intermittent pain and locking of a digit in flexion of finger flexor tendons</td>
</tr>
</tbody>
</table>

ESR = erythrocyte sedimentation rate
like a stocking. It is extremely strong laterally where it becomes the illiotibial band. Where it crosses the hip, trochanteric bursitis can occur. The lateral femoral condyle of the knee can also be a site of tendinitis as well, particularly in runners. Trochanteric bursitis and illiotibial band syndrome are two conditions which respond well to corticosteroid injections and a rehabilitation program aimed at stretching this musculotendinous band. They are commonly mistaken for lumbosacral radiculopathy.

Pain at the bottom of the foot with symptoms of burning and tingling is frequently plantar fasciitis. Dorsiflexing the foot and palpating the plantar fascia will identify taut painful tendinous bands if plantar fasciitis is present.

Neuralgic amyotrophy from diabetes is a condition that is often difficult to distinguish from lumbosacral radiculopathy. It often presents with thigh pain and on EMG appears more like proximal lumbosacral plexus mononeuropathies with frequent involvement of the femoral nerve. Diabetic thoracic radiculopathy is a distinct syndrome with abdominal wall or thoracic wall pain, and weight loss, but has a good prognosis. In diabetic thoracic radiculopathy, intra-abdominal and intra-thoracic conditions must first be excluded. The EMG findings of denervation in the abdominal or thoracic wall musculature are consistent with this clinical entity.

Mononeuropathies such as peroneal, tibial, and femoral, pose diagnostic challenges and the EDX consultant should sample enough muscles with EMG in different peripheral nerve distributions to confirm that findings are not localized to a particular peripheral nerve distribution.

**PHYSICAL EXAMINATION**

The EDX examination is an extension of the standard clinical examination. The history and physical examination are vital initial steps in determining what conditions may be causing the patient’s symptoms. Most radiculopathies present with symptoms in one limb. Multiple radiculopathies such as are seen in cervical spinal stenosis or lumbar stenosis, may cause symptoms in more than one limb. A focused neuromuscular examination that assesses strength, reflexes, and sensation in the affected limb and the contralateral limb provides a framework for EDX assessment.

An algorithmic approach to utilizing physical examination and symptom information to tailor the EDX evaluation is shown in Figure 1. In this approach, the patient’s symptoms, and physical examination signs of sensory loss and weakness create a conceptual framework for approaching these sometimes daunting problems. Admittedly, there are many exceptions to this approach with considerable overlap in conditions which might fall in multiple categories. Radiculopathies and entrapment neuropathies are examples of such conditions with a variety of clinical presentations and physical examination findings, such that they are included in both focal symptom categories with and without sensory loss. In the case of a person with lumbosacral radiculopathy, a positive straight leg raise test may be noted in the absence of motor, reflex, or sensory changes. Conditions such as myopathies and polyneuropathies better fit this algorithmic approach given that symptoms and physical examination signs are somewhat more specific. Figure 1 also contains musculoskeletal disorders and denotes how they fall into this conceptual framework. The EDX physician must be willing to modify the EDX examination in response to nerve conduction and EMG findings and adjust the focus of the examination in light of new information.

The implications of symptoms and signs on EDX findings were investigated by Lauder and colleagues for cohorts of patients with upper or lower limb symptoms as well suspected cervical and lumbosacral radiculopathies. Even though physical examination findings were better at predicting who would have a radiculopathy, many patients with normal examinations had abnormal EMG studies, indicating that clinicians should not curtail EDX testing simply because the physical examination is normal. For lower limb

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical symptoms/signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibromyalgia syndrome and polymyalgia rheumatica</td>
<td>As in Table 1</td>
</tr>
<tr>
<td>Hip arthritis</td>
<td>Pain in groin, anterior thigh, pain with weight bearing, positive Patrick's test</td>
</tr>
<tr>
<td>Trochanteric bursitis</td>
<td>Lateral hip pain, pain with palpation on lateral and posterior hip</td>
</tr>
<tr>
<td>Iliotibial band syndrome</td>
<td>Pain along outer thigh, pain with palpation</td>
</tr>
<tr>
<td>Knee arthritis</td>
<td>Pain with weight bearing</td>
</tr>
<tr>
<td>Patellofemoral pain</td>
<td>Anterior knee pain, worsen with prolonged sitting</td>
</tr>
<tr>
<td>Pes anserinus bursitis</td>
<td>Medial proximal tibia pain, tender to palpation</td>
</tr>
<tr>
<td>Hamstring tendinitis, chronic strain</td>
<td>Posterior knee and thigh pain, can mimic positive straight leg raise, common in runners</td>
</tr>
<tr>
<td>Baker's cyst</td>
<td>Posterior knee pain and swelling</td>
</tr>
<tr>
<td>Plantar fasciitis</td>
<td>Pain in sole of foot, worsened with weight bearing activities, tender to palpation</td>
</tr>
<tr>
<td>Gastrocnemius-soleus tendinitis</td>
<td>Calf pain, worsened with sports activities, usually limited range of motion compared to asymptomatic limb, chronic strain</td>
</tr>
</tbody>
</table>
Evaluating the Patient With Suspected Radiculopathy

AANEM Course

Symptoms, loss of a reflex or weakness dramatically increased the likelihood of having a radiculopathy by EMG. Losing the Achilles reflex for instance, resulted in an odds ratio of 8.4 (p<0.01)—8 times the likelihood of having a radiculopathy (S1 level) by EMG with this physical examination finding.35 Weakness in any leg muscle group resulted in about 2.5 times greater chance of identifying a lumbar radiculopathy on EMG.35

Similar findings were noted for upper limb symptoms. For instance, if a reflex was lost or weakness was noted, the likelihood of having a cervical radiculopathy confirmed by EMG was about 4 times more likely.36 Combinations of findings, particularly weakness plus reflex changes, resulted in a 9-fold greater likelihood of cervical radiculopathy.36

Guidelines for Radiculopathy Evaluation

The American Association of Neuromuscular & Electrodiagnostic Medicine’s (AANEM) guidelines recommend that for an optimal evaluation of a patient with suspected radiculopathy, a needle EMG screen of a sufficient number of muscles and at least one motor and one sensory nerve conduction study (NCS) should be performed in the involved limb.1 The NCSs are necessary to exclude polyneuropathy. The sufficiency of the EMG screen and a recommended number of muscles is discussed in detail below. An EMG study is considered confirmatory for a radiculopathy if EMG abnormalities are found in two or more muscles innervated by the same nerve root and different peripheral nerves, yet muscles innervated by adjacent nerve roots are normal.66 This definition assumes that other generalized conditions such as polyneuropathy are not present.

Bilateral limbs are often necessary to study, particularly if a single limb shows EMG findings suggestive of radiculopathy and the patient has symptoms in both the studied and the contralateral limb. If bilateral limbs are involved, the EDX physician should have a low threshold for studying selected muscles in an upper limb (if the lower limbs are abnormal on EMG) or a lower limb (if both upper limbs are abnormal), to exclude a generalized process such as polyneuropathy or motor neuron disease. Likewise, additional NCSs are appropriate to exclude other suspected conditions and the EDX consultant should have a low threshold for expanding the study.

H Reflexes, F Waves, and NCSs

NCSs, H reflexes, and F waves are not very useful for confirming radiculopathy. They are useful, however, to exclude polyneuropathy or mononeuropathies.
H Reflexes

H reflexes have commonly been used to determine whether a radiculopathy demonstrates S1 involvement. It is a monosynaptic reflex that is an S1 mediated response and can differentiate to some extent L5 from S1 radiculopathy. Many researchers have evaluated their sensitivity and specificity with respect to lumbosacral radiculopathies and generally found a range of sensitivities from 32-88%. However, many of these studies suffered from lack of a control group, imprecise inclusion criteria, or small sample sizes.

Marin and colleagues prospectively examined the H reflex and the extensor digitorum brevis reflex in 53 normal subjects, 17 patients with L5, and 18 patients with S1 radiculopathy. Patients included in the study had all of the following: (1) radiating low back pain into the leg; (2) reduced sensation or weakness or positive straight leg raise test; and (3) either EMG evidence of radiculopathy or structural causes of radiculopathy on magnetic resonance imaging (MRI) or computed tomography (CT) imaging. The H-reflex maximal side-to-side latency difference was 1.8 ms as derived from the normal group. They analyzed the sensitivity of the H reflex for side-to-side differences greater than 1.8 ms or a unilaterally absent H reflex on the affected side. The H reflex on the affected side. The H reflex only demonstrated a 50% sensitivity for S1 radiculopathy and 6% for L5 radiculopathy, but had a 91% specificity. Amplitudes were not assessed in this study. These results suggest that the H reflex has a low sensitivity for S1 root level involvement.

H reflexes may be useful to identify subtle S1 radiculopathy, yet there are a number of shortcomings related to these responses. They can be normal with radiculopathies, and because they are mediated over such a long physiological pathway, they can be abnormal due to polyneuropathy, sciatic neuropathy, or plexopathy. They are most useful in the assessment for polyneuropathy.

In order to interpret a latency or amplitude value and render a judgement as to the probability that it is abnormal, precise population-based normative values encompassing a large age range of normal subjects must be available for NCS comparisons. Falco and colleagues demonstrated in a group of healthy elderly subjects (60-88 years old), that the tibial H reflex was present and recorded bilaterally in 92%. Most elderly subjects are expected to have normal H-reflex studies and when abnormalities are found in these persons, the EDX consultant should critically evaluate these findings and the clinical scenario before attributing H-reflex abnormalities to the aging process.

F Waves

F waves are late responses involving the motor axons and axonal pool at the spinal cord level. They can be assessed and classified by using the minimal latency, mean latency, and chronodispersion or scatter. As in the case of H reflexes, they demonstrate low sensitivities and are not specific for radiculopathy, rather they are a better screen for polyneuropathy. Published sensitivities range from 13-69%, however these studies suffer from many of the shortcomings described for H-reflex studies.

London and England reported two cases of persons with neurogenic claudication from lumbosacral spinal stenosis. They demonstrated that the F-wave responses could be reversibly changed after 15 minutes of ambulation which provoked symptoms. This suggested an ischemia-induced conduction block in proximal motor neurons. A larger scale study of this type might find a use for F waves in the identification of lumbosacral spinal stenosis and delineate neurogenic from vascular claudication.

Motor and Sensory NCSs

Standard motor and sensory NCSs may not be helpful in identifying a cervical or lumbosacral radiculopathy, however they should be performed to screen for polyneuropathy and exclude common entrapment neuropathies if the patient's symptoms could be explained by a focal entrapment.

Plexopathies often pose a diagnostic challenge, as they are similar to radiculopathies in symptoms and signs. In order to distinguish plexopathy from radiculopathy, sensory responses which are accessible in a limb should be tested. In plexopathy, they are likely to be reduced in amplitude, whereas in radiculopathy they are generally normal. If substantial axonal loss has occurred at the root level, the CMAP recorded in muscles innervated by that root may be reduced in both plexopathies and radiculopathies. This is usually when severe axonal loss has occurred such as with cauda equina lesions or penetrating trauma that severely injures a nerve root. The distal motor latencies and conduction velocities are usually preserved as they reflect the fastest conducting nerve fibers.

SOMATOSENSORY EVOKED POTENTIALS, DERMATOMAL SOMATOSENSORY EVOKED POTENTIALS, AND MAGNETIC EVOKED POTENTIALS

The AANEM guidelines examined the literature and concluded that somatosensory evoked potentials (SEPs) may be useful for cervical spondylosis with cord compression. Likewise, in lumbosacral spinal stenosis, dermatomal somatosensory evoked potentials (DSEPs) may be useful in defining levels of deficits.

Physiological evidence of multiple or single root involvement in lumbosacral spinal stenosis can be documented with DESPs and may be useful in the case where spinal canal narrowing is minimal and the patient has symptoms. This testing also complements standard needle EMG. Snowden and colleagues found that for single and multilevel lumbosacral spinal stenosis, DSEP revealed 78% sensitivity relative to spinal imaging. In this well-designed prospective study, DSEP criteria as well as inclusion criteria were precisely defined. The predictive value for a positive test was 93%.

Yiannikas, Shahani, and Young demonstrated that SEPs may be useful for cervical myelopathy. In this study, in 10 patients with clinical signs of myelopathy, all 10 had abnormal peroneal SEPs and 7 had abnormal median SEPs.
Maertens de Noordhout and colleagues examined motor and SEPs in 55 persons with unequivocal signs and symptoms of cervical spinal myelopathy. In this group 87% showed gait disturbances, and 82% showed hyperreflexia. MRI was not the diagnostic standard as these authors felt that MRI was prone to overdiagnosis; metrizamide myelography showed unequivocal signs of cervical cord compression for all patients. Magnetic stimulation of the cortex was performed and the responses measured with surface electrodes. In these subjects 89% demonstrated abnormalities in motor evoked potentials (MEP) to the first dorsal interosseus muscle and 93% had one MEP abnormality. At least one SEP abnormality was noted in 73%. This study demonstrated the potential usefulness of these techniques for identifying subtle cord compression.

Tavy and colleagues examined whether MEPs or SEPs assisted in identifying persons with radiological evidence of cervical cord compression but who were without clinical markers for myelopathy. All patients had clinical symptoms of cervical radiculopathy, but not myelopathy. In this group MEPs were normal in 92% and SEPs were normal in 96%. These investigators concluded that MEPs and SEPs are normal in most cases of persons with asymptomatic cervical stenosis. This indicates that abnormal MEPs and SEPs are likely to be true positive findings and not false positives related to mild asymptomatic cord compression. It is important to remember that cervical spondylisis is a process that causes a continuum of problems including both radiculopathy and myelopathy.

The inherent variability and difficulty in determinations as to what constitutes normal evoked potentials prompted investigation. Dumitru and colleagues examined the variations in latencies with SEPs. In 29 normal subjects, they examined the ipsilateral intertrial variations, arithmetic mean side-to-side differences and maximum potential side-to-side differences with stimulation of the superficial peroneal sensory nerve, sural nerve and L5 and S1 dermatomes with respect to P1 and N1 latencies and peak-to-peak amplitudes. Considerable ipsilateral intertrial variation was observed and side-to-side comparisons revealed a further increase in this inherent variation regarding the above measured parameters. They suggested an additional parameter with which to evaluate SEPs: the maximum side-to-side latency difference.

Dumitru and colleagues, in a study involving persons with unilateral and unilevel L5 and S1 radiculopathies, evaluated dermatomal and segmental SEPs. History, physical examination, imaging studies, and EDX medicine evaluations clearly defined patients with unilateral/unilevel L5 or S1 nerve root compromise. Regression equation analysis for cortical P1 latencies evaluating age and height based on comparable patient and control reference populations revealed segmental and dermatomal sensitivities for L5 radiculopathies to be 70% and 50%, respectively, at 90% confidence intervals. Similar sensitivities were obtained for 2 standard deviation mean cortical P1 latencies. Side-to-side cortical P1 latency difference data revealed segmental and dermatomal sensitivities for S1 radiculopathies to be 50% and 10%, respectively, at 2 standard deviations. These investigators questioned the clinical utility of both segmental and dermatomal SEPs in the evaluation of patients with suspected unilateral/unilevel L5 and S1 nerve root compromise, finding little utility for these tests in persons with single level lumbosacral radiculopathy.

**PURPOSE OF EDX TESTING**

EDX testing is expensive and uncomfortable for patients, therefore, it is important to understand why it is performed and the expected outcomes. EDX testing serves several important purposes:

- It effectively excludes other conditions that mimic radiculopathy such as polyneuropathy or entrapment neuropathy. Haig and colleagues demonstrated that the referring diagnostic impression is often altered with EDX testing.
- EDX testing can to some extent suggest severity, or extent of the disorder beyond the clinical symptoms. Involvement of other extremities can be delineated or the involvement of multiple roots may be demonstrated, such as in the case of lumbosacral spinal stenosis.
- There is utility in solidifying a diagnosis. An unequivocal radiculopathy on EMG in an elderly patient with nonspecific or mild lumbar spondylisis or stenosis on MRI reduces diagnostic uncertainty and identifies avenues of management such as lumbar corticosteroid injections or decompression surgery in certain situations.
- Outcome prediction may be possible. If surgical intervention is planned for a lumbosacral radiculopathy, a positive EMG preoperatively improves the likelihood of a successful outcome postoperatively. This is an area that deserves more research attention.

**EMG AND DIAGNOSTIC SENSITIVITIES**

The need for EMG, particularly in relationship to imaging of the spine, has been recently highlighted. Needle EMG is particularly helpful in view of the fact that the false positive rates for MRI of the lumbar spine are high, with 27% of normal subjects having a disc protrusion. For the cervical spine the false positive rate for MRI is much lower with 19% of subjects demonstrating an abnormality, but only 10% showing a herniated or bulging disc. Radiculopathies can occur without structural findings on MRI, and likewise without EMG findings. The EMG only evaluates motor axonal loss or mild lumbar spondylisis or stenosis on MRI reduces diagnostic uncertainty and identifies avenues of management such as lumbar corticosteroid injections or decompression surgery in certain situations.
The sensitivity of EMG for cervical and lumbosacral radiculopathies has been examined in a number of studies. The results of some of these studies are tabulated in Table 3. Table 3 lists the “gold standards” against which these EMG findings were compared. Studies using a clinical standard may reflect a less severe group, whereas those using a surgical confirmation may indicate a more severely involved group. The sensitivity for EMG is unimpressive, ranging from 49-92% in these studies. EMG is not a sensitive test, yet it likely has a higher specificity. The issue of specificity and its value in EDX was underscored by Robinson.9 It is apparent that EMG is not a good screening test. In terms of screening tests, MRI is better for identifying subtle structural abnormalities, with EMG to assess their clinical relevance and exclude other disorders.

PARASPINAL MUSCLE EXAMINATION

Paraspinal muscles (PM) are important to study for a variety of reasons but there are some important caveats regarding their examination. In one study, Date and colleagues demonstrated that lumbar paraspinal muscles in asymptomatic subjects over 40 years old showed denervation potentials approximately 30% of the time.7 Nardin and colleagues similarly noted up to 48% of normal subjects having fibrillations or positive sharp waves in at least one site with the prevalence higher for those over 40 years of age.44

In sharp contrast to these findings, Dumitru, Diaz, and King examined the lumbosacral paraspinal muscles and intrinsic foot muscles with monopolar EMG.15 These investigators recorded potentials and found that there were irregularly firing potentials with similar waveform characteristics as fibrillations and positive sharp waves (PSW). By excluding irregularly firing potentials (atypical endplate spikes) they found much lower false positive paraspinal findings than the investigators above, with only 4% of their normal subjects showing regularly firing fibrillations or PSW potentials. They felt that the higher prevalences of spontaneous activity previously reported were due to not fully appreciating the similarity between innervated and denervated spontaneous single muscle fiber discharges. This quantitative study underscores the need to assess both firing rate and rhythm as well as discharge morphology when evaluating for fibrillations and positive waves in the lumbar paraspinal muscles. EDX physicians should take care not to over-diagnose paraspinal muscle EMG findings by mistaking irregularly firing endplate spikes for fibrillations.

PM may be abnormal in patients with spinal cancers,4,32,33 or amyotrophic lateral sclerosis,60 and following spinal surgery44 or lumbar puncture.7

Investigations over the last decade have provided insights into better quantification and examination of lumbosacral PMs. The lumbar PM examination has been refined through investigations that used a grading scale for the findings.19,20,21,22 The “mini PM” score provides a quantitative means of deriving the degree of PM denervation.19 It distinguishes normal findings from EMG findings in persons with radiculopathy. This novel and quantitative technique may prove to identify subtle radiculopathies or spinal stenosis with greater precision.

Identification as a separate concept from sensitivity

Because EDX is a composite assessment composed of various tests, a fundamental question is when the point of diminishing returns has been reached. Some radiculopathies cannot be confirmed by needle EMG, even though the signs and symptoms along with imaging results suggest that radiculopathy is the correct diagnosis. A screening EMG study involves determining whether or not the radiculopathy can be confirmed by EMG. If the radiculopathy cannot be confirmed, then presumably no amount of muscles can identify the radiculopathy. If it can be confirmed, then the screen should identify this possibility with a high probability. The process of identification can be conceptualized as a conditional probability: Given that a radiculopathy can be confirmed by needle EMG, what is the minimum number of muscles which must be examined in order to confidently recognize or exclude this possibility? This is a fundamentally different concept from sensitivity. It involves understanding and defining the limitations of a composite test (group of muscles).

How many and which muscles to study

The concept of a screening EMG encompasses identifying the possibility of an EDX-confirmable radiculopathy. If one of the muscles in the screen is abnormal, the screen must be expanded to exclude other diagnoses, and to fully delineate the radiculopathy level. Because of the screening nature of the EMG examination, EDX physicians with experience should look for more subtle signs of denervation, and if present in the screening muscles, then expand the study to determine if these findings are limited to a single myotome or peripheral nerve distribution. If they are limited to a single muscle, the clinical significance is uncertain.

The Cervical Radiculopathy Screen

Dillingham and colleagues conducted a prospective multi-center study evaluating patients referred to participating EDX laboratories with suspected cervical radiculopathy.10 A standard set of muscles were examined by needle EMG for all patients. Those with electrodiagnostically confirmed cervical radiculopathies, based upon EMG findings, were selected for analysis. The EMG findings in this prospective study also encompassed other neuropathic findings: (1) positive sharp waves, (2) fibrillation potentials, (3) complex repetitive discharges, (4) high-amplitude, long-duration motor unit action potentials, (5) increased polyphasic motor unit action potentials, or (6) reduced recruitment. There were 101 patients with EDX confirmed cervical radiculopathies representing all cervical root levels. When paraspinal muscles were one of the screening muscles and neuropathic findings were assessed, five muscle screens identified 90-98% of radiculopathies, 6 muscle screens identified 94-99% and seven muscle screens identified 96-100% (Tables 4 and 5). When paraspinal muscles were not part of the screen, eight distal limb muscles recognized 92-95% of radiculopathies. Without paraspinal muscles, the identification rates were consistently lower. If one only considers fibrillations and positive sharp waves in the EMG assessment, identification rates are lower.
Six muscle screens including paraspinal muscles yielded consistently high identification rates and studying additional muscles lead to marginal increases in identification. Individual screens useful to the EDX physician are listed in Tables 4 and 5. In some instances a particular muscle cannot be studied due to wounds, skin grafts, dressings, or infections. In such cases the EDX physician can use an alternative screen with equally high identification. These findings were consistent with those derived from a large retrospective study.33

The Lumbosacral Radiculopathy Screen

A prospective multicenter study was conducted at five institutions by Dillingham and colleagues.10 Patients referred to participating EDX laboratories with suspected lumbosacral radiculopathy were recruited and a standard set of muscles examined by needle EMG. Patients with EDX-confirmed lumbosacral radiculopathies were selected for analysis. As described above for the prospective cervical study, neuropathic findings were analyzed along with spontaneous activity. There were 102 patients with EDX confirmed lumbosacral radiculopathies representing all lumbosacral root levels. When paraspinal muscles were one of the screening muscles, 4 muscle screens identified 88-97%, 5 muscle screens identified 94-98%, and 6 muscle screens 98-100% (Tables 6, 7, and 8). When paraspinal muscles were not part of the screen, identification rates were lower for all screens and eight distal muscles were necessary to identify 90%. As with cervical radiculopathy screens, assessing for neuropathic findings increases identification rates. If only four muscles can be tested due to limited patient tolerance, as seen in Table 6, and if one of these muscles are the paraspinals, few EDX-confirmable radiculopathies will be missed. A large retrospective study noted similar findings, concluding that five muscles identified most electrodiagnostically confirmable radiculopathies.37

Dillingham and Dasher9 re-analyzed data from a study published by Knutsson almost 40 years earlier.29 In this detailed study, 206 patients with sciatica, underwent lumbar surgical exploration. All subjects underwent a standardized 14 muscle EMG evaluation by the author (Knutsson) using concentric needles. The examiner was blinded to other test results and physical examination findings. In addition to the EMG and surgical information, myelogram and physical examination data were derived. In this re-analysis, screens of four muscles with one being the lumbosacral paraspinal muscle yielded (1) an identification rate of 100%, (2) a 92% sensitivity with respect to the intraoperative anatomical nerve root compressions, and (3) an 89% sensitivity with respect to the clinical inclusion criteria.9 This study, using data from 4 decades ago, confirmed that a 4 muscle screen provides high identification. These findings are consistent with contemporary work showing that screens with relatively few muscles (five or six) are sufficient.

As described above, recent research efforts were undertaken to refine and streamline the EMG examination. The strongest studies, contemporary prospective multicenter investigations, provide the best estimates of a sufficient number of muscles.10,11 In summary, for both cervical and lumbosacral radiculopathy screens the optimal number of muscles appears to be six muscles which include the paraspinal muscles and represent all root level innervations. When paraspinal muscles are not reliable, then eight nonparaspinal muscles must be examined.

Another way to think of this:
To minimize harm, six in the leg and six in the arm.
If one of the six muscles studied in the screen is positive with a neuropathic finding, there exists the possibility of confirming EDX that a radiculopathy is present. In this case, the examiner must study additional muscles. Nerve conductions should be undertaken as well to determine if this muscle finding is due to a mononeuropathy. If more extensive EMG testing reveals that the findings are limited to a single muscle, and NCSs exclude mononeuropathy, then the single muscle finding remains inconclusive and of uncertain clinical relevance.

If none of the six muscles are abnormal, the examiner can be confident in not missing the opportunity to confirm by EDX that a radiculopathy is present. In this case, the examiner must study additional muscles. Nerve conductions should be undertaken as well to determine if this muscle finding is due to a mononeuropathy. If more extensive EMG testing reveals that the findings are limited to a single muscle, and NCSs exclude mononeuropathy, then the single muscle finding remains inconclusive and of uncertain clinical relevance.

If none of the six muscles are abnormal, the examiner can be confident in not missing the opportunity to confirm by EDX that a radiculopathy is present. In this case, the examiner must study additional muscles. Nerve conductions should be undertaken as well to determine if this muscle finding is due to a mononeuropathy. If more extensive EMG testing reveals that the findings are limited to a single muscle, and NCSs exclude mononeuropathy, then the single muscle finding remains inconclusive and of uncertain clinical relevance.

**Table 4** Five muscle screen identifications of patients with cervical radiculopathies

<table>
<thead>
<tr>
<th>MUSCLE SCREEN</th>
<th>NEUROPATHIC</th>
<th>SPONTANEOUS ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Without Paraspinals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>deltoid, APB, FCU, triceps, PT</td>
<td>92%</td>
<td>65%</td>
</tr>
<tr>
<td>biceps, triceps, EDC, FCR, FDI</td>
<td>85%</td>
<td>54%</td>
</tr>
<tr>
<td>deltoid, triceps, EDC, FDI, FCR</td>
<td>84%</td>
<td>58%</td>
</tr>
<tr>
<td>biceps, triceps, PT, APB, FCU</td>
<td>91%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>With Paraspinals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>deltoid, triceps, PT, APB, PSM</td>
<td>98%</td>
<td>80%</td>
</tr>
<tr>
<td>biceps, triceps, EDC, FDI, PSM</td>
<td>95%</td>
<td>73%</td>
</tr>
<tr>
<td>deltoid, EDC, FDI, PSM, FCU</td>
<td>90%</td>
<td>73%</td>
</tr>
<tr>
<td>biceps, FCR, APB, PT, PSM</td>
<td>95%</td>
<td>77%</td>
</tr>
</tbody>
</table>

The screen detected the patient with cervical radiculopathy if any muscle in the screen was one of the muscles which were abnormal for that patient. Neuropathic findings for non-paraspinal muscles included positive waves, fibrillations, increased polyphasic potentials, neuropathic recruitment, increased insertional activity, CRDs, or large amplitude long duration motor unit action potentials. For paraspinal muscles the neuropathic category included fibrillations, increased insertional activity, positive waves, or CRDs. Spontaneous activity referred only to fibrillations or positive sharp waves.

APB = abductor pollicis brevis; CRD = complex repetitive discharge; EDC = extensor digitorum communis; FCR = flexor carpi radialis; FCU = flexor carpi ulnaris; FDI = first dorsal interosseous; PSM = cervical paraspinal muscles; PT = pronator teres. (Adapted with permission, Dillingham and colleagues. Identification of cervical radiculopathies: optimizing the electromyographic screen. Am J Phys Med Rehabil 2001;80:84-91.)

**LUMBAR SPINAL STENOSIS**

There are fewer studies examining spinal stenosis and EMG. For lumbosacral spinal stenosis, Hall and colleagues showed that 92% of persons with imaging confirmed stenosis had a positive EMG. They also underscored the fact that 46% of persons with a positive EMG study did not demonstrate PM abnormalities, only distal muscle findings. For 76% of patients, the EMG showed bilateral myotomal involvement.

**LIMITATIONS OF THE NEEDLE EMG SCREEN**

These cervical and lumbosacral muscle screens should not substitute for a clinical evaluation and differential diagnosis formulation by the EDX physician. Rather, the information from investigations described earlier in the article allows the EDX consultant to streamline the EMG evaluation and make more informed clinical decisions regarding the probability of missing an EDX-confirmable radiculopathy when a given set of muscles are studied. Performing a focused history and physical
examination is essential, and these screens should not supplant such clinical assessments or a more detailed EDX study when circumstances dictate.

It is important to remember that the EMG screens for cervical and lumbosacral radiculopathies were validated in a group of patients with limb symptoms suggestive of radiculopathies. These screens will not provide sufficient screening power if a brachial plexopathy is present or if a focal mononeuropathy such as a suprascapular neuropathy is the cause of the patient’s symptoms. The EDX physician should always perform EMG on weak muscles to increase the diagnostic yield. The six muscle EMG tests do not sufficiently screen for myopathies or motor neuron disease. It is incumbent upon the EDX physician to formulate a differential diagnosis and methodically evaluate for the diagnostic possibilities, further refining the examination as data are acquired.

### Table 6 Four muscle screen identifications of patients with lumbosacral radiculopathies.

<table>
<thead>
<tr>
<th>muscle Screen</th>
<th>Neuropathic Activity</th>
<th>Spontaneous Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Four Muscles</strong> Without Paraspinals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATIB, PTIB, MGAS, RFEM</td>
<td>85%</td>
<td>75%</td>
</tr>
<tr>
<td>VMED, TFL, LGAS, PTIB</td>
<td>75%</td>
<td>58%</td>
</tr>
<tr>
<td>VLAT, SHBF, LGAS, ADD</td>
<td>52%</td>
<td>35%</td>
</tr>
<tr>
<td>ADD, TFL, MGAS, PTIB</td>
<td>80%</td>
<td>67%</td>
</tr>
<tr>
<td><strong>Four Muscles</strong> With Paraspinals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATIB, PTIB, MGAS, PSM</td>
<td>97%</td>
<td>90%</td>
</tr>
<tr>
<td>VMED, LGAS, PTIB, PSM</td>
<td>91%</td>
<td>81%</td>
</tr>
<tr>
<td>VLAT, TFL, LGAS, PSM</td>
<td>88%</td>
<td>77%</td>
</tr>
<tr>
<td>ADD, MGAS, PTIB, PSM</td>
<td>94%</td>
<td>86%</td>
</tr>
</tbody>
</table>

The screen identified the patient if any muscle in the screen was abnormal for that patient. The muscle either demonstrated neuropathic findings or spontaneous activity. Neuropathic findings for non-paraspinal muscles included positive waves, fibrillations, increased polyphasic potentials, neuropathic recruitment, increased insertional activity, CRDs, or large amplitude long duration motor unit action potentials. Spontaneous activity referred only to fibrillations or positive sharp waves. For paraspinal muscles the neuropathic category included fibrillations, increased insertional activity, positive waves, or CRDs.

ADD = adductor longus; ATIB = anterior tibialis; CRD = complex repetitive discharge; LGAS = lateral gastrocnemius; MGAS = medial gastrocnemius; PSM = lumbosacral paraspinal muscles; PTIB = posterior tibialis; RFEM = rectus femoris; SHBF = short head biceps femoris; TFL = tensor fascia lata; VLAT = vastus lateralis; VMED = vastus medialis. (Adapted with permission from Dillingham and colleagues. Identification of cervical radiculopathies: optimizing the electromyographic screen. Am J Phys Med Rehabil 2001;80: 84-91) 10

### Table 7 Five muscle screen identifications of patients with lumbosacral radiculopathies

<table>
<thead>
<tr>
<th>Screen</th>
<th>Neuropathic Activity</th>
<th>Spontaneous Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Five Muscles Without Paraspinals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATIB, PTIB, MGAS, RFEM, SHBF</td>
<td>88%</td>
<td>77%</td>
</tr>
<tr>
<td>VMED, TFL, LGAS, PTIB, ADD</td>
<td>76%</td>
<td>59%</td>
</tr>
<tr>
<td>VLAT, SHBF, LGAS, ADD, TFL</td>
<td>68%</td>
<td>50%</td>
</tr>
<tr>
<td>ADD, TFL, MGAS, PTIB, ATIB</td>
<td>86%</td>
<td>78%</td>
</tr>
<tr>
<td><strong>Five Muscles With Paraspinals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATIB, PTIB, MGAS, PSM, VMED</td>
<td>98%</td>
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<td>97%</td>
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<tr>
<td>VLAT, TFL, LGAS, PSM, ATIB</td>
<td>97%</td>
<td>86%</td>
</tr>
<tr>
<td>ADD, MGAS, PTIB, PSM, VLAT</td>
<td>94%</td>
<td>86%</td>
</tr>
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</table>

ADD = adductor longus; ATIB = anterior tibialis; CRD = complex repetitive discharge; LGAS = lateral gastrocnemius; MGAS = medial gastrocnemius; PSM = lumbosacral paraspinal muscles; PTIB = posterior tibialis; RFEM = rectus femoris; SHBF = short head biceps femoris; TFL = tensor fascia lata; VLAT = vastus lateralis; VMED = vastus medialis.

### SPECIFICITY OF THE EMG SCREEN

Tong and colleagues, 61 examined the specificity in persons age 55 and older who were asymptomatic. A standardized EDX study was conducted by a blinded EDX physician using a monopolar needle to assess five leg muscles and the paraspinal muscles.

There were 30 subjects with a mean age of 65.4 yrs (SD 8.0). When only positive sharp waves or fibrillations were counted as abnormal, (two limb muscles plus associated lumbar paraspinal muscle abnormal, two limb muscles abnormal, or one limb muscle plus associated lumbar paraspinal muscle abnormal) a 100% specificity was noted in most of the diagnostic criteria. When at least 30% polyphasia in the limb muscles was considered as abnormal, the respective specificities were 97%, 90%, and 87%. The specificity for plexopathy was 100% when only positive sharp waves or fibrillations were used, and it remained 100% when increased polyphasia was added. This study demonstrated that needle EMG has excellent specificity for lumbosacral radiculopathy and plexopathy when the appropriate diagnostic criteria are used. 61

### SYMPTOM DURATION AND THE PROBABILITY OF FIBRILLATIONS

Previously, a well-defined temporal course of events was thought to occur with radiculopathies despite the absence of studies that support such a relationship between symptom duration and the probability of spontaneous activity in a muscle. It was a common belief that in acute lumbosacral radiculopathies, the paraspinal muscles denervated first, followed by distal muscles, and that later reinnervation began with paraspinal muscles and then with distal muscles. This paradigm...
was recently challenged by a series of investigations.12,13,14,48 For both EDX-confirmed lumbosacral and cervical radiculopathies, symptom duration had no significant relationship to the probability of finding spontaneous activity in paraspinal or limb muscles.

The findings from these investigations underscored the fact that the pathophysiological processes involved with cervical and lumbosacral radiculopathies are complex.12,13,14,48 Diagnostic EMG findings, manifested as a result of these processes, cannot be predicted by this overly simplistic, symptom-duration explanation. Symptom duration should not be invoked to explain the presence or absence of paraspinal or limb muscle spontaneous activity in persons suspected of having a radiculopathy.

**IMPLICATIONS OF AN ELECTRODIAGNOSTICALLY CONFIRMED RADICULOPATHY**

It is important that the EDX physician not forget that EMG does not indicate the exact cause of the symptoms, only that axonal loss is taking place. A spine tumor, herniated disc, bony spinal stenosis, inflammatory radiculitis, or severe spondylolysis can all yield the same EMG findings. This underscores the need to image the spine with MRI to assess for significant structural causes of electrodiagnostically confirmed radiculopathy. A negative EMG test should not curtail obtaining an MRI if clinical suspicion for radiculopathy is high. Given the low sensitivities of needle EMG, it is not an optimal screening test, but rather a confirmatory and complementary test to spinal imaging.

There are few studies that examine outcomes and the usefulness of EDX in predicting treatment success, the exception being surgical outcomes for lumbar discectomy. Tullberg and colleagues evaluated 20 patients with lumbosacral radicular syndromes who underwent unilevel surgery for disc herniations.63 They evaluated these patients before surgery and 1 year later with lower limb EMG, NCS, F waves, and SEPs. They showed that the EDX findings did not correlate with the level defined by computerized tomography for 15 patients. However, those patients in whom EDX testing preoperatively was normal were significantly more likely to have a poor surgical outcome (p<0.01). In spite of the fact that the sample size in this study was small, the significant correlation of a normal EDX study with poor outcome suggests that this may be a true relationship.

Spengler and Freeman described an objective approach to the assessment of patients preoperatively for laminectomy and discectomy for lumbosacral radiculopathy.57 Spengler and colleagues confirmed and underscored these previous findings regarding objective methods to assess the probability of surgical success preoperatively.58 In this preoperative screening evaluation, the EMG findings were combined with imaging, clinical, and psychological assessments. The EMG findings figured prominently (one quarter of the scale) — those patients with positive EMGs were more likely to have better surgical outcomes. This was particularly true when the EMG findings correlated with the spinal imaging findings in a person without psychological or dysfunctional personality issues.

**Figure 2** Implications of a positive or negative electromyography (EMG) screening evaluation. Note that a positive result will usually warrant further EMG testing to fully define the pathology, and a negative test could lead to nerve conduction or other testing to consider other diagnoses. PSM = paraspinal muscles; MRI = magnetic resonance imaging. (Modified from Dillingham TR. Electrodiagnostic approach to patients with suspected radiculopathy. Phys Med Rehabil Clin N Am 2002;13:567-588, with permission.)
It has become apparent over the last 2 decades that the natural history of both lumbosacral radiculopathy and cervical radiculopathy, with or without structural findings on MRI, is very favorable. A classic investigation by Henrik Weber showed that surgery for a herniated nucleus pulposis causing sciatica was more effective at pain control at 1 year, but beyond that conservative treatment had equal results compared to the surgically managed group. Of particular note was the fact that weakness did not correlate with outcome and even for persons with motor weakness, a good outcome with conservative treatment was the norm, and surgery did not improve motor return. Other investigators in cohort outcome studies demonstrated that the majority of persons suffering lumbosacral radiculopathy can resolve their symptoms. In fact, on follow-up MRI studies, lumbosacral disc herniations and disc fragments resolve in 76% of patients. The outcomes for cervical radiculopathy are generally good in the absence of myelopathy.

Saal, Saal, and Yurth demonstrated that persons with cervical disc herniations have a similar favorable clinical course as persons with lumbosacral radiculopathy. These patients were managed with pain management strategies incorporating medications, rehabilitation with cervical traction and exercises, and epidural or selective nerve root injections if medications failed to control pain. In this series, the majority of patients (24 of 26) achieved successful outcomes.

**SUMMARY**

One cannot minimize the importance of the clinical evaluation and differential diagnosis formulation by the EDX physician to guide testing. The needle EMG examination is the most useful EDX test but is limited in sensitivity. EMG screening examinations using six muscles are possible that optimize identification yet minimize patient discomfort. EMG findings must be interpreted relative to the patient’s clinical presentation, and the consultant should tailor the EDX study to the clinical situation. EMG complements spinal imaging and often raises other diagnostic possibilities in addition to confirming clinical suspicions.

### REFERENCES

10. Dillingham and colleagues TR, Lauder TD, Andary M, Kumar S, Pezzin LE, Stephens RT, Shannon S. Identification of cervical ra-


INTRODUCTION

Symptoms of numbness and tingling are common neurologic complaints. The evaluation of a peripheral neuropathy (PN) can seem daunting given the long list of potential causes and the number of available diagnostic tests, including antibody and genetic test panels. However, the evaluation is manageable using a structured approach. This manuscript presents elements of such an approach based on a systematic evaluation of symptoms and signs and electrodiagnostic (EDX) findings (Table 1). Clinical characterization is achieved by asking direct historical questions and conducting thoughtful clinical tests. The role of EDX testing is stressed because it provides unique information on the pathologic features of the neuropathy not otherwise available from symptoms and clinical signs. The process is divided into 7 steps. With a full characterization, the list of potential causes becomes shorter and the appropriate selection of informative tests more manageable. This approach, in various forms, has been described elsewhere.\(^{11,12,14}\)

As clinical features are elicited, it is important to appreciate that not all symptoms of numbness, sensory loss, and weakness are due to peripheral nerve disease. The exercise of neurologic localization is an essential element to assure peripheral nervous system (PNS) pathology. The most common errors in localization are failure to diagnose central nervous system pathology and somatization. Clinical features suggestive of a myelopathy include numbness that does not follow a stocking-glove or dermatomal distribution (numbness involving both legs to the waist or above), numbness affecting one limb or side of the body, and pathologic tendon reflexes. In these circumstances, other diagnostic tests can help confirm central nervous system involvement.

Sensory symptoms attributable to somatization are common but challenging because the clinician does not want to miss a neurologic disease. However, it is equally inappropriate to carry forward a tentative neurologic diagnosis that is not tenable. One approach is to determine whether the symptoms make sense anatomically (based on the organization of the peripheral or central nervous systems) or pathophysiologically (based on types of peripheral nerve and central nervous system pathology). EDX studies can determine the presence of PNS involvement. If there is no evidence for a neurologic basis for the symptoms, a gentle but frank discussion into issues in a patient’s life is appropriate.

This manuscript will focus on peripheral neuropathies. Disorders primarily affecting other portions of the PNS, such as radiculopathies and plexopathies, will not be considered.

PERTINENT PNS ANATOMY

A simple working view of PNS anatomy is useful when evaluating for a peripheral neuropathy. The PNS can be divided into autonomic and somatic components. Autonomic nerve fibers markedly outnumber somatic fibers, but symptoms and signs of autonomic nerve dysfunction are rare compared to those associated with somatic nerve dysfunction. When present, prominent autonomic signs provide an important clue to specific causes of a neuropathy, but most diagnostic efforts focus on somatic nerves.

Step 1

The first step when evaluating a patient with suspected PN is determining if there is involvement of sensory nerves, motor nerves, or both. The distribution of nerve involvement may not be obvious from symptoms, but can be determined accurately by EDX studies. This can be explained by the fact that damage to sensory nerves results in more frequent symptoms than damage to motor nerves.
Damage to sensory nerves disrupts connections between receptors and nerve endings leading to altered function and sensory symptoms. The same degree of damage to motor nerves may not affect strength because collateral reinnervation of denervated muscle fibers preserves motor function and obscures symptoms. Furthermore, most neuropathies affect distal lower extremity muscles first, and weakness of toe flexion will not be readily apparent to the patient. An additional factor is that sensory nerves have both peripheral and central branches, and damage to distal portions of sensory fibers represents a double disconnection.

Many neuropathies are described by their symptoms, at times emphatically so (“a pure sensory or pure motor neuropathy”), when in fact there may be evidence for both motor and sensory nerve involvement. It is important for the physician to gather all the data and assess and classify neuropathies based on their pathological involvement and not solely on symptoms.8

### Table 1  Questions to address in a structured approach to evaluating peripheral neuropathies

<table>
<thead>
<tr>
<th>Step 1: Which parts of the peripheral nervous system?</th>
<th>Somatic, autonomic, both Motor, sensory, both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2: What is the distribution?</td>
<td>Distal predominant Distal and proximal Dermatomal Radicular Plexopathy</td>
</tr>
<tr>
<td>Step 3: What is the time course?</td>
<td>Rate of progression (acute, chronic, insidious)</td>
</tr>
<tr>
<td>Step 4: What are the clinic findings?</td>
<td>Symptoms Signs Physical features (high arches, hammer toes) Medical conditions (contributing diseases, drugs) Family history</td>
</tr>
<tr>
<td>Step 5: What is the underlying pathology?</td>
<td>Primary axonal, primary demyelinating (conduction block)</td>
</tr>
<tr>
<td>Step 6: Are there underlying medical conditions?</td>
<td>Diseases (diabetes, renal failure, collagen vascular) Surgeries (barosurgery)</td>
</tr>
<tr>
<td>Step 7: Is there a family history of a polyneuropathy?</td>
<td>History of foot deformities or gait difficulties Examination of suspected family members</td>
</tr>
</tbody>
</table>

### Step 2

The second step is determining the distribution of involvement (Table 2). Peripheral neuropathies (PNs) most commonly follow one of several general patterns. Polyneuropathies are roughly symmetric in distribution and tend to affect nerves in a length dependent manner, with longest nerves first (stocking-glove distribution). Polyradiculoneuropathies include nerve roots as well as peripheral nerves, leading to diffuse symptoms in both proximal and distal distributions. Mononeuropathies involve the distribution of a single nerve with motor and sensory disturbance in a nerve distribution. Mononeuritis multiplex may become confluent and relatively symmetric, but a step-wise progression can usually be elicited from the history. Neuropathies that do not follow these patterns are important to recognize, and the pathology may be identifiable based on their unusual pattern.

### TIME COURSE

#### Step 3

Every disease has a momentum or time course. The third step is determining the time course to help focus the differential diagnosis (Table 3). Acute neuropathies progress over days to several weeks, while chronic neuropathies progress over many months to years, and may have an insidious onset.

### Table 2 Patterns of peripheral nerve involvement and examples of neuropathies.

<table>
<thead>
<tr>
<th>Symmetric, length dependent distribution</th>
<th>Diabetes Drugs Toxins Metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetric, proximal and distal distribution</td>
<td>Acute inflammatory demyelinating polyradiculoneuropathy Chronic inflammatory demyelinating polyradiculoneuropathy</td>
</tr>
<tr>
<td>Asymmetric, nerve or plexus distribution</td>
<td>Diabetic amyotrophy Idiopathic plexopathy Mononeuritis multiplex</td>
</tr>
<tr>
<td>Asymmetric, unusual</td>
<td>Porphyria Leprosy Tangier disease Multifocal motor conduction block neuropathy</td>
</tr>
<tr>
<td>Autonomic, unusual</td>
<td>Amyloidosis</td>
</tr>
</tbody>
</table>
proximal amyotrophy with a polyneuropathy.3 Mononeuritis multiplex in the setting of symmetric distal sensory loss suggests diabetic amyotrophy (CIDP). Acute onset of asymmetric painful proximal neuropathy suggests chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), also known as Guillain-Barré syndrome, includes symptoms involving both distal and proximal limbs with progression over 2 to 4 weeks.20 A similar distribution of distal and proximal symptoms and signs, but progressing over several months, suggests chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Acute onset of asymmetric painful proximal neuropathy in the setting of symmetric distal sensory loss suggests diabetic proximal amyotrophy with a polyneuropathy.3 Mononeuritis multiplex is suggested by a stepwise progression involving single nerve distributions. The majority of neuropathies will be chronic. A symmetric motor and sensory neuropathy with an ill-defined insidious onset raises the question of a familial neuropathy, and it is important to seek evidence for involvement in childhood and other family members.

**SUMMARY OF DIAGNOSTIC STEPS 1-3**

The site of initial involvement, the distribution of involvement, and the pattern of progression can be combined. For example, a pattern suggesting acute inflammatory demyelinating polyradiculoneuropathy (AIDP), also known as Guillain-Barré syndrome, includes symptoms involving both distal and proximal limbs with progression over 2 to 4 weeks.20 A similar distribution of distal and proximal symptoms and signs, but progressing over several months, suggests chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Acute onset of asymmetric painful proximal neuropathy in the setting of symmetric distal sensory loss suggests diabetic proximal amyotrophy with a polyneuropathy.3 Mononeuritis multiplex is suggested by a stepwise progression involving single nerve distributions. The majority of neuropathies will be chronic. A symmetric motor and sensory neuropathy with an ill-defined insidious onset raises the question of a familial neuropathy, and it is important to seek evidence for involvement in childhood and other family members.

**CLINICAL FEATURES**

**Step 4**

The fourth step in the evaluation is determining the clinical features, including symptoms and signs, physical aspects, identification of potential underlying medical conditions, drug use, and family history.

**Symptoms**

Elicitation of a full spectrum of symptoms is helpful in narrowing diagnostic possibilities and guiding symptomatic treatment. Neuropathic symptoms may be positive or negative in nature (Table 4).24,27 Positive symptoms imply spontaneous discharges in nerve fibers, while negative symptoms imply loss of normally conducted discharges. Positive sensory symptoms are easily recognized and are frequently volunteered by the patient as chief complaints. Positive motor symptoms may not be recognized by the patient, and should be actively sought because they may be the only clinical manifestation of motor nerve involvement. The discrepancy between patient perception of sensory and motor symptoms is due to two factors. First, collateral reinnervation occurs with loss of motor fibers, which tends to preserve muscle strength, whereas the same degree of sensory fiber loss is essentially permanent and symptomatic. Second, mild weakness of distal muscles (intrinsic foot muscles) does not usually affect motor function to a noticeable degree.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Examples of acute and chronic neuropathies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (days to weeks)</td>
<td>Acute inflammatory demyelinating polyradiculoneuropathy</td>
</tr>
<tr>
<td></td>
<td>Porphyria</td>
</tr>
<tr>
<td></td>
<td>Acute toxic exposure (arsenic)</td>
</tr>
<tr>
<td></td>
<td>Mononeuritis multiplex</td>
</tr>
<tr>
<td></td>
<td>Proximal diabetic neuropathy</td>
</tr>
<tr>
<td></td>
<td>Idiopathic plexopathy</td>
</tr>
<tr>
<td></td>
<td>Paraneoplastic sensory neuropathy</td>
</tr>
<tr>
<td>Chronic (months to years)</td>
<td>Diabetic polyneuropathy</td>
</tr>
<tr>
<td></td>
<td>Chronic inflammatory demyelinating polyradiculoneuropathy</td>
</tr>
<tr>
<td></td>
<td>Charcot-Marie-Tooth hereditary neuropathy</td>
</tr>
<tr>
<td></td>
<td>Idiopathic</td>
</tr>
</tbody>
</table>

**Table 4** Examples of positive and negative sensory and motor symptoms

<table>
<thead>
<tr>
<th>Sensory Symptoms</th>
<th>Motor Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Paresthesias</td>
<td>Fasciculations</td>
</tr>
<tr>
<td>Pain (burning, squeezing, electric-like, hyper sensitivity)</td>
<td>Cramps</td>
</tr>
<tr>
<td>Negative Numbness</td>
<td>Reduced or lack of sensation</td>
</tr>
<tr>
<td>Postural instability</td>
<td>Weakness</td>
</tr>
<tr>
<td>Atrophy</td>
<td></td>
</tr>
</tbody>
</table>

**Sensory Signs**

Clinical testing of sensory function is a subjective endeavor. Although attempts are made to assess a number of individual sensory modalities and nerve fiber types, distinctions between modalities and fiber types may be more apparent than real. While there are examples of large fiber neuropathies (Friedreich’s ataxia) and small fiber neuropathies (Tangier’s disease), most sensory modalities (light touch through pain) can be conveyed by both large and small diameter fibers. Further, clinical testing (light touch, stroking, sharp instruments) usually activates a variety of receptor types. An important clinical variable is patient attention. It is advisable to develop an individual set of tests that are informative. It is important to not become bogged down in incongruities during the examination with a large battery of tests.

The following information is offered as a guide to selecting a set of clinical sensory tests. Findings from formal psychophysical laboratory testing of sensory perception should be combined with a set of informative clinical tests of sensory function.10 A variety of cutaneous receptor types subserve low-threshold mechanoreception, and mechanoreceptors are most sensitive to moving stimuli. In formal testing, controlled stimuli are applied to restricted areas of skin. In contrast, clinical testing of mechanoreception may include touch or stroking, and likely activates a variety of receptor types. Psychophysical testing for vibration perception confirms equal sensitivity for frequencies from 64 Hz to 512 Hz. Nociceptive stimulation is perhaps the most challenging. It is difficult to separate stimulus properties of nociception from pressure and it is possible for a subject to distinguish a sharp from a dull stimulus without feeling pain. Nociceptive stimuli are felt to be conveyed by “small fibers,” but some nociceptive...
receptors are innervated by myelinated fibers. Formal testing of noxious stimuli has been by hot and cold stimuli using special equipment, and it is not clear how well temperature detection can be assessed with clinical testing using the cold end of a tuning fork.

Reliable and informative results can be obtained from the clinical tests listed below.

**Touch threshold.** Patient detection of the lightest touch or stroking on the dorsum of the hand and foot represents a measure of low threshold sensory perception. Use of a 10 g filament is another method to distinguish light touch thresholds.

**Vibration threshold.** Patient perception of when a tuning fork applied to a finger or toe dies out is a measure of vibration threshold. Vibration perception is felt to represent large fiber function. A 128 Hz tuning fork dies out more slowly than a 256 Hz fork and is easier to use. The patient must understand the need to indicate complete disappearance. The time interval (in seconds) from when the vibration extinguishes in the patient compared to the observer is a measure of impairment.

**Sharp stimulus threshold.** A patient’s ability to distinguish between the lightly applied “pokey” feeling from the sharp end of a safety pin compared to the similarly lightly applied dull end likely represents discrimination of more noxious stimuli from light touch.

**Position threshold.** Patient perception of changes in joint position is usually exquisite. Any errors in direction, or false perception of movement, are abnormal.

The tests of light touch, the distinguishing the sharp end of the safety pin, and position sense should be performed with the patient blinded to the exercise.

The sensory examination can be focused to answer several useful clinical questions. Most information about the neuropathy should come from the patient’s history, and the sensory examination should be confirmatory. Two questions to consider for a symmetric polyneuropathy are the presence of a distal-to-proximal gradient, and the severity of nerve damage. Patients can contribute to determining sensory gradient and severity. It is surprising how readily a patient can mark a point on their limb below which sensation is abnormal and above which it is normal. The gradient can be confirmed clinically by asking if light touch is perceived less strongly at a distal point compared to a proximal point. Severity of light touch loss can be addressed by asking the patient to estimate the relative percent value of light touch sensation at the involved site compared to the face. Severity of vibration loss can be estimated by the time difference between vibration extinguishing for the patient compared to the examiner.

Questions to consider for an asymmetric neuropathy are whether the sensory loss follows a nerve distribution, a radicular distribution, or a complex pattern best explained by a plexopathy.

**Tendon reflexes.** An objective measure of sensory nerve function is the deep tendon reflex. The deep tendon reflex is a monosynaptic reflex arc with sensory and motor nerve components, but the arc is much more vulnerable to sensory nerve damage. As an example, ankle plantar flexion strength is relatively preserved in all but the most severe neuropathies, yet ankle reflexes are lost early on. Accordingly, an absent Achilles tendon reflex is an objective indication of a significant degree of sensory nerve damage. It is important to be assured that the reflex is truly absent by performing a number of reinforcing maneuvers while testing.

**Motor Signs**

Motor signs include muscle atrophy and weakness. Mild distal atrophy can be appreciated by assessing the prominence of extensor tendons in the feet and finding a thin foot. Prominent tendons and thin feet suggest loss of intrinsic foot muscle bulk. A certain amount of denervation and atrophy occur with age, which must be considered. Weakness can be appreciated by testing muscles that can be just overcome in normal individuals. Accordingly, flexion and extension of the lesser toes and extension of the great toe are informative when weakness is subtle. Ankle dorsiflexion weakness will occur with greater severity of the neuropathy, but it is rare for plantar flexion to be weak until very late in a neuropathy. The angle between the shin and the foot is a clue to distal weakness: in normal individuals it is about 130 degrees, but with weakness of anterior muscles, the angle increases and can be 180 degrees in the setting of a neuropathy. Fallen arches also suggest intrinsic foot weakness. In the hands, atrophy of the first dorsal interosseous muscle and weakness of finger abduction are informative.

**Orthopedic Signs**

Inspection of the foot for high arches and hammertoes is informative because it suggests a long-standing neuropathy. The shape of the foot is determined by the interplay of muscular forces acting on the various bones in the foot. Weakness of extensor muscles leads to a foreshortened foot (high arches) and hammertoes.22

**Autonomic Signs**

As discussed earlier, autonomic nerve fibers make up the majority of fibers in a nerve but account for a minority of symptoms. Evidence for autonomic nerve dysfunction comes from symptoms of orthostatic dizziness and impotence in men. Clinical signs of autonomic dysfunction are an orthostatic blood pressure change. Dry and scaly skin on the feet is a clue to autonomic dysfunction. Dry eyes and mouth (sicca syndrome) represent reduced tear and salivary gland activity, and raise the question of Sjögren’s syndrome that can be associated with sensory neuropathies.

**PN NERVE PATHOLOGY**

**Step 5**

Underlying pathologic processes are poorly understood for most neuropathies. However, the consequences of the processes can be viewed clinically as causing three patterns of PN damage: primary
axonal, primary demyelinating, and a combination of the two. The fifth step is determining the predominant pathologic process. Primary axonal damage usually follows a distal predominant pattern because longer nerves tend to be affected first. This results in symptoms and signs in a distal-to-proximal gradient that can be demonstrated clinically by a stocking-glove distribution, with more pronounced abnormalities distally than proximally within a limb, and more in legs than in arms. Primary demyelination can occur at multiple foci along nerves, leading to both distal and proximal involvement at onset or early in the course, that can be demonstrated clinically by finding both distal and proximal weakness and sensory disturbance. In addition, demyelinating polyradiculoneuropathies involve roots of nerves innervating both proximal and distal muscles and skin. Demyelinating neuropathies usually include a variable degree of axonal damage, and the distinction between primary demyelination and a combination of demyelination and axonal damage can be challenging. EDX studies are helpful in making this distinction.

Mononeuropathies generally have axonal pathology. An exception is asymmetric neuropathies characterized by focal conduc-
tion block. The distinction between axonal and conduction block mononeuropathies can be made with EDX testing.

Collateral reinnervation represents an important compensatory mechanism in peripheral neuropathies. Loss of motor nerve axons initiates sprouting of terminal branches from intact axons to rein-
nervate denervated muscle fibers. This compensates and preserves muscle strength until 50% or more motor axons degenerate, at which time reinnervation can not keep up and the muscle becomes clinically weak. This means that muscle strength is not a sensitive measure of whether motor nerves are involved in a peripheral neu-
ropathy. Needle electromyography (EMG), however, is sensitive to the process of reinnervation.

**EDX Features**

Perhaps the most important element in the diagnostic evaluation is EDX testing because nerve conduction and needle EMG studies provide objective information on the peripheral nervous system not available from the history and clinical examination. Characterization by EDX features can thus narrow the differential diagnostic list. EDX test results are considered from two directions: by the EDX physician conducting the study, and by the consultant reviewing an existing study. The performance and interpretation of EDX studies can be optimized for both the performer and reviewer by following several principles. The EDX test should be used as a direct extension of the neurologic examination to answer specific questions: (1) Confirm which portions of the PNS are involved; sensory only, motor only, or both. In this regard, step 5 complements step 1; (2) Confirm the distribution of involvement: symmetric polyneuropathy, single nerves, or another pattern; (3) Determine the pathologic mecha-
nism: primary axonal, primary demyelination, or a mixture; (4) Determine the severity and time course: mild or severe, recent or chronic.

### Nerve Conduction Studies

**Primary axonal loss and demyelination.** The question of underlying pathology is the most challenging question to answer. Distinctions are based primarily on motor nerve conduction velocity values. Nerve conduction measures of distal latency, conduction velocity and F-wave latency focus on the fastest conducting fibers. Experience indicates that severe axonal loss has relatively little effect on nerve conduction. Changes in conduction can be expressed as percentages of the laboratory limits of normal: lower limits of normal (LLN) for conduction velocity, and upper limits of normal (ULN) for distal latency and F-wave latency. Thus in amyotrophic lateral sclerosis, as an example of a pure and severe axonal motor neuropathy, distal latencies are rarely longer than 125% of the ULN, conduction veloc-
ties rarely slower than 70% of the LLN, and F-wave latencies rarely longer than 125% of the ULN.

The distinction between demyelinating and axonal pathology is based on showing a degree of slowed conduction greater than ex-
pected for axonal loss alone. Just how slow is slower than expected has been the subject of controversy. Several sets of nerve conduction limits for primary demyelination have been proposed and tested. The problem of sensitivity and specificity looms large because some demyelinating neuropathies are mild, and nerve conduction values will overlap with normal values and abnormal values encountered in axonal neuropathies. Table 5 lists nerve conduction guidelines for considering primary demyelination.

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Limits of Axonal Pathology</th>
<th>Limits of Demyelinating Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal latency</td>
<td>&lt;120% ULN</td>
<td>&gt;130% ULN</td>
</tr>
<tr>
<td>Conduction velocity</td>
<td>&gt;70% ULN</td>
<td>&lt;70% ULN</td>
</tr>
<tr>
<td>Proximal: distal amplitude</td>
<td>&lt;50%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Abnormal temporal dispersion</td>
<td>Smooth waveform</td>
<td>Irregular waveform</td>
</tr>
<tr>
<td>F-wave latency</td>
<td>&lt;130% ULN</td>
<td>&gt;130% ULN</td>
</tr>
</tbody>
</table>

**Demyelination and conduction block.** Although distal latency, conduction velocity, and F-wave latency measure the speed of the fastest conducting fibers, it is possible to assess the conduction speed of the remainder of the fibers in the response by looking for abnormal temporal dispersion. Quantitatively, temporal dispersion can be assessed by the duration of the negative compound muscle action potential (CMAP) waveform. Temporal dispersion represents the spectrum of arrival times of nerve impulses from the range of nerve fiber conduction velocities. Abnormal temporal dispersion is caused by a greater degree of slowing of individual nerve fibers due to
An Approach to the Patient With Peripheral Neuropathy

Demyelination. Abnormal temporal dispersion leads to a greater degree of phase cancellation in the waveform leading to a reduction of the amplitude of the CMAP to more proximal stimulation compared to the amplitude following more distal stimulation. If individual nerve fibers slow to a halt, i.e., conduction block, there will also be a reduction of the CMAP amplitude to more proximal stimulation, and thus a drop in amplitude of the proximal response by greater than 50% indicates increased temporal dispersion and greater phase cancellation, or conduction block, or both. There are guidelines to help distinguish between abnormal temporal dispersion and conduction block (Table 6). In abnormal temporal dispersion there will be an amplitude reduction of the proximal response but little change in the areas of the response. In addition, there will be a prolongation of the negative peak duration. In conduction block there will be a reduction of both amplitude and area with little change in the negative peak duration. However, many clinical examples include a combination of abnormal temporal dispersion and conduction block. What is most important is that abnormal temporal dispersion and conduction block suggests a demyelinating pathology.

Table 6  Nerve conduction value guidelines to help distinguish between abnormal temporal dispersion, conduction block, or a combination of the two

<table>
<thead>
<tr>
<th></th>
<th>CMAP Amplitude</th>
<th>CMAP Negative Peak Area</th>
<th>CMAP Negative Peak Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conduction block</td>
<td>&lt;50%</td>
<td>&lt;50%</td>
<td>≤30%</td>
</tr>
<tr>
<td>Conduction block/Abnormal temporal dispersion</td>
<td>&lt;50%</td>
<td>&lt;50%</td>
<td>&gt;30%</td>
</tr>
<tr>
<td>Temporal dispersion</td>
<td>&lt;50%</td>
<td>&gt;50%</td>
<td>&gt;30%</td>
</tr>
</tbody>
</table>


Abnormal temporal dispersion can be assessed qualitatively because it will also affect the smooth shape of the CMAP waveform, and wave form irregularities should be sought by inspection (Figure 1). Assessing for abnormal temporal dispersion is important because a group of hereditary neuropathies, Charcot-Marie-Tooth type 1, are characterized by slow conduction velocity but no abnormal temporal dispersion (Figure 2).

**Needle EMG**

The needle EMG examination is important because it is the most sensitive measure of motor nerve involvement. CMAP amplitude is a measure of axonal loss, but collateral reinnervation will compensate early for mild degrees of loss, and CMAP amplitude will not be a sensitive measure of early loss. The presence of abnormal temporal dispersion (fibrillation potentials and positive waves) is sensitive signs of denervation. Reduced motor unit recruitment indicates a neuropathic cause of denervation. The chronicity of

Figure 1  Differences between normal and abnormal temporal dispersion stimulating at the wrist, elbow, and axilla.

Left set of waveforms: Normal changes in motor responses with greater conduction distances due to normal temporal dispersion. Right set of waveforms: Marked changes in motor responses with greater conduction distances due to abnormal temporal dispersion. Note initial low response amplitude with further loss with greater conduction distances, and irregularities of the waveform. Oscilloscope settings: 5 ms/div and 5 mV/div.

Figure 2  Motor nerve conduction study stimulating at the wrist and elbow showing slow conduction velocity with normal temporal dispersion in Charcot-Marie-Tooth hereditary neuropathy type 1A.

Top set of waveforms: Slow velocity (18 m/s) from subject with Charcot-Marie-Tooth hereditary neuropathy type 1A with normal changes in waveforms reflecting normal temporal dispersion. Bottom set of waveforms: Normal velocity (52 m/s) with normal changes in waveforms reflecting abnormal temporal dispersion. Oscilloscope settings: 5 ms/div and 5 mV/div.
motor nerve loss can be assessed by the degree of complexity of the motor unit action potentials; highly complex or polyphonic potentials support an ongoing enervating process, while high amplitude but simple potentials support a very longstanding enervating process. In the latter situation, a longstanding and slowly progressive denervation lends support for a hereditary neuropathy.

SUMMARY OF DIAGNOSTIC STEPS 1-5

At the conclusion of the clinical and EDX evaluation (steps 1-5), a full characterization of the peripheral neuropathy should emerge (Table 7). The differential diagnostic list is relatively short under each type of neuropathy.8 At this point, a review of the medical and family histories can be incorporated to give a complete characterization and a meaningful series of laboratory tests can be ordered.

MEDICAL HISTORY

Step 6

There are long lists of medical conditions and drugs that cause or predispose to peripheral neuropathy, but careful review reveals that some associations are rare and may reflect chance occurrences. Step 6 is to assess possible factors. In practical terms, a limited number of systemic diseases relate to peripheral neuropathies. Diabetes is the most common underlying disease, not only for frank diabetes, but also for undocumented diabetes (impaired glucose tolerance).23 Renal failure is also a cause of neuropathy, but not until the creatinine level is over 5 mg/dl.2 Diseases of the gastrointestinal tract are uncommonly associated with PNs, and inflammatory bowel diseases are rarely a factor.1 Gastric resection or stapling procedures may predispose to vitamin B12 deficiency.1,15 Other vitamin deficiencies are rare in North America. On the other hand, vitamin B6 toxicity can occur at doses readily available to health and nutrition enthusiasts.5 Ethanol as a neurotoxin in a well-nourished individual is controversial, and is probably uncommon in all but chronic heavy users.13,16 Thyroid dysfunction is also controversial. Hypothyroidism is common, but there are few well-documented examples of polyneuropathy attributed to mild thyroid dysfunction.26 Rheumatologic disorders can be associated with vasculitic neuropathies.

Medication use, both current and past, should be sought for a number of compounds. Cancer chemotherapeutic drugs such as cisplatin, vincristine, and the taxols are neurotoxic. There is a question whether previous exposure to neurotoxic chemotherapeutic drugs can be a predisposing factor for neuropathies from another cause, and has been shown to occur for vincristine in the setting of Charcot-Marie-Tooth type 1A hereditary neuropathies.14 Among commonly used drugs, nitrofurantoin and amiodarone can be neurotoxic. Infrequently used neurotoxic drugs include disulfiram, gold, and isoniazid. Recreational inhaled compounds, including n-hexane in glue sniffing should also be considered.25

FAMILY HISTORY

Step 7

It is likely that hereditary neuropathies account for a larger than appreciated percentage of mild and very chronic idiopathic neuropathies. Step 7 assesses this possibility.9 Interestingly, among large families with known hereditary neuropathies, only 20% of affected family members seek medical attention because of symptoms. Accordingly, a full family history with detailed queries to the patient and relatives (if necessary over the telephone) about symptoms and signs that may suggest a hereditary neuropathy can be fruitful (Table 8).

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OTHER DIAGNOSTIC TESTS

A number of ancillary diagnostic tests are available for special circumstances. These tests should be ordered when there is evidence from the history and examination findings that they will be informative. Lumbar puncture for cerebral spinal fluid can be informative for evidence of breakdown of the blood-nerve barrier by elevated protein when root involvement is suspected, as in AIDP and CIDP. Abnormal cells can suggest other processes, such as an infectious process. Peripheral nerve biopsy can provide evidence for vasculitis, amyloidosis, and infiltrative conditions. Skin biopsies can confirm damage to intraepidermal nerve endings. Recently, tests for antibodies against various gangliosides and for paraneoplastic conditions have become widely available. Antibody tests should be ordered with caution because the diagnostic yield of these tests is low.

SUMMARY

At the conclusion of the evaluation that includes a full characterization and a rational set of diagnostic tests a diagnosis should be forthcoming. However, it should be kept in mind that despite best efforts, it is important to appreciate that a good percentage of neuropathies, perhaps 20%, will remain undiagnosed despite an exhaustive evaluation. Ordering more laboratory tests is seldom informative, and may lead to false positive findings. A periodic review of a patient’s history and inquiry for new symptoms may be helpful.

REFERENCES

LOCALIZATION OF THE PROBLEM USING HISTORY AND EXAMINATION

Numbness can be the result of a disease process located in the central nervous system (CNS) or the peripheral nervous system (PNS). It can often be localized by the patient’s history alone. It is important to recognize both the timing and onset of the patient’s symptoms and the distribution of the patient’s signs and symptoms. Localizing a patient’s deficits to a specific area of the nervous system frequently can be accomplished with attention to the distribution of symptoms (e.g., right versus left, arm versus leg, proximal versus distal, symmetric versus asymmetric, and the presence of facial involvement). Determining the characteristics of symptoms (sensory and motor or sensory) and the temporal features (acute or chronic, or static or progressive) is also helpful.

Obtaining a clear history is important. The patient’s complaints of “numbness” can include a range of sensory disturbances. The patient can describe “tingling,” “burning,” or a true loss of sensation simply as “numbness.” It is important to be specific when questioning the patient to clearly define the range of symptoms. This will help in identifying the etiology of the disease process. The simultaneous evaluation of the distribution of these complaints can significantly refine the differential diagnosis. Recognition of the common symptoms may have a major impact on appropriate treatment and may allow early management which can minimize long-term residual deficits for the patient. The use of a questionnaire with a human figure is helpful in defining the symptoms and their distribution (Figure 1).

The extent and characteristics of the patient’s symptoms are related to the specific portion of the nervous system injured. Different populations of neurons are vulnerable in specific disease processes. The vulnerability may arise from the effect of a disease on a specific vascular territory (e.g., stroke, vasculitis, aneurysm), a space occupying lesion (e.g., tumor, herniated disk) or an autoimmune, inflammatory attack on the nervous system. Taking the patient’s history can frequently help the physician determine the localization (Tables 1 and 2).
A Practical Approach to the Patient Presenting With Numbness

The distribution of lesions affecting the CNS are usually distinct from those affecting the PNS (Table 3).

This manuscript explores the possible disorders that can cause numbness along the neuroaxis, starting at the brain and moving out to the spinal cord and then peripheral nerves.

**BRAIN**

Numbness may be secondary to a lesion of the parietal lobe or thalamus (ventral posteromedial nucleus). Thalamic lesions produce contralateral sensory loss and numbness, but these may be painful. An abrupt onset suggests a cerebral vascular event and may be seen with lacunar infarcts secondary to hypertension. The patient would typically have sudden onset of contralateral sensory loss without other weakness. A magnetic resonance imaging (MRI) scan may confirm the presence of a lacunar infarct or a hemorrhagic infarction. Relative to other brain regions, the thalamus is more vulnerable to hemorrhage resulting from hypertension in the brain.

Parietal lobe lesions cause contralateral numbness associated with loss of discriminatory sensation. The patient may feel touch but may not localize it well. Patients may experience weakness as well as numbness but sensory complaints are more prominent.

**SPINAL CORD**

Lesions in the spinal cord resulting only in numbness are not common. Most cause both numbness and weakness. This is due to the close proximity of motor and sensory neurons and their pathways in the spinal cord and existing nerve roots. Inflammatory lesions can selectively affect sensory pathways. This can result in profound sensory disturbances that are typically bilateral. Disorders such as acute myelitis and multiple sclerosis can present as primarily sensory disturbances.

**NERVE ROOT/DORSAL ROOT GANGLION**

Sensory and motor nerve roots are separate as they exit the spinal cord but combine at the level of the dorsal root ganglion. The most common cause of nerve root injury is due to a herniated vertebral disk. This typically results in radiating pain frequently with both motor and sensory fibers involved. The involvement in the dermatome of multiple nerve roots suggests a problem other than a structural lesion. Consideration must be given to an inflammatory, neoplastic, or infectious process.

Selective involvement of the dorsal root ganglion cells causes a profound sensory loss. The differential diagnosis of a dorsal root ganglionopathy is a short list which includes heavy metals and paraneoplastic syndromes.

| Table 1 Patient’s description of sensory loss likelihood of the localization |
|---|---|
| Tingling | PNS > CNS |
| Burning | PNS > CNS |
| Total loss of feeling | CNS* > PNS** |
| Poor coordination*** | CNS = PNS |

*CNS = central nervous system; PNS = peripheral nervous system
* Localization to the central nervous system would most commonly involve unilateral signs and symptoms except with spinal cord lesions where symptoms are usually bilateral.
** Peripheral nervous system lesions can be either multifocal or, commonly, bilateral and symmetric. Early signs in a neuropathy may involve only one extremity (usually the feet) but peripheral involvement would be much less likely with all unilateral complaints.
*** Poor coordination can result from either central (cerebellar, brainstem) or peripheral (impaired proprioception, nerve, dorsal root ganglion) pathology.

| Table 2 Distribution and characteristics of patient complaints along the neuraxis |
|---|---|---|---|
| Distribution | Facial Involvement | Characteristic | Pain |
| Brain | Unilateral | often | sensory + motor | no |
| Spinal Cord | Bilateral | no | sensory + motor | poss. |
| Nerve Root | Unilateral | no | sensory + motor | yes |
| Nerve | Unilateral or Bilateral | possible | sensory, motor, autonomic or combo | yes |
| Neuromuscular Junction | often bilateral | yes, but not always | motor | no |
| Muscle | Bilateral | rare | motor | rare |
Peripheral nerve injury is the most common reason for sensory disturbances, especially numbness. However, peripheral nerve injury frequently presents with both motor and sensory symptoms. The causes for a predominantly sensory neuropathy can be better understood if upon presentation the salient features of the patient’s sensory complaints are recognized. The goal is to distinguish between small fiber sensation (e.g., light touch, pain, and temperature) and large fiber sensation (e.g., position sensation and partial vibratory sensation).

The list of possible etiologies that result in sensory neuropathy is long. It is also important to recognize some distinguishing features of the patient’s sensory disturbance, such as past history and family history. Diabetes, alcohol abuse, chronic use of medication or vitamins, and history of similar sensory problems in the family are significant clues to identifying a proper etiology. In the United States and many European countries, diabetes is the most common cause of neuropathy. However, leprosy remains the most common cause of neuropathy worldwide. The etiologies can be categorized as toxic, immune, metabolic, inherited, or mechanical.

**HISTORY OF THE PRESENT ILLNESS**

Knowing the timing of the onset of the symptoms as well as the family history and any occupational exposures can be helpful in understanding the disease process and fine-tuning the evaluation.

**Onset**

A slow, progressive numbness or sensory disturbance is frequently described as distal numbness or tingling in the toes. This may progress proximally into the feet and then up the legs and involve the hands as well (i.e., a stocking/glove distribution). The most distal segments of the nerve are most dependent upon axonal transport for delivery of vital proteins and neurotransmitters. Any process that interrupts axonal flow will be recognized by the patient as a symptom in the most distal aspects of the affected nerve. A slow progression from distal to proximal would strongly suggest a peripheral neuropathy in the differential diagnosis. Sensory complaints due to nerve root compression or irritation can also progress slowly. However, these lesions are commonly characterized by pain in the affected root distribution. The sensory complaints from a nerve root injury or generalized neuropathy can be episodic, particularly earlier in their course. Sensory disturbances from brain or spinal cord injury (typically vascular events) usually evolve more acutely. Numbness or paresthesias due to multiple sclerosis typically happens over days and may be episodic.

An acute or subacute onset with rapid progression of sensory complaints, accompanied usually by weakness, is consistent with localization to the brain, spinal cord, nerve root, or nerve. Typically, ischemic injury is associated with sudden onset of sensory symptoms. Inflammatory disorders can develop quickly and progress over several days and can affect any part of the neuraxis. In the brain, acute onset of sensory symptoms is typically accompanied by weakness and/or encephalopathy. The differential diagnoses would include stroke, multiple sclerosis, cancer (lymphoma, metastasis), and infection. In the nerve root, acute sensory symptoms are likely due to compression from a disk or trauma. In the peripheral nerve, the possible etiologies are more extensive but some require timely and appropriate management. Acute inflammatory demyelinating polyneuropathy often requires prompt management to maintain the airway and initiate treatment. Arsenic, thallium, tick paralysis, and porphyria are other problems that start with numbness but may result in a rapidly progressive disability for the patient and require urgent treatment (Table 4).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Etiologic classifications affecting the central versus. peripheral nervous system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>Vascular</td>
<td>stroke, arterial-venous malformation claudication</td>
</tr>
<tr>
<td>Structural</td>
<td>tumor, disk infection, vasculitis</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>myopathy, motor neuron disease</td>
</tr>
<tr>
<td>Genetic</td>
<td>Multiple sclerosis, myelopathy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Considerations of differential diagnosis for neuropathy in patients with sensory complaints using the onset and progression as criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACUTE (Days)</td>
<td>CHRONIC (Weeks - Months)</td>
</tr>
<tr>
<td>Immune</td>
<td>Guillain-Barré &amp; variants, Vasculitis</td>
</tr>
<tr>
<td>Toxins</td>
<td>Botulism, Buckthorn, Diphtheria, Tick, Arsenic, Organophosphates, Thallium, Vacor</td>
</tr>
<tr>
<td>Drugs</td>
<td>Captopril (few case reports), Chemotherapeutic Agents</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Porphyria</td>
</tr>
<tr>
<td>Nutritional</td>
<td>Vitamin toxicity or deficiency</td>
</tr>
<tr>
<td>Hereditary</td>
<td>Hereditary motor and sensory neuropathy hereditary sensory neuropathy</td>
</tr>
</tbody>
</table>
**Family History**

Family history can be helpful in identifying the etiology of neuropathy, particularly if a family member has had symptoms similar to the patient’s problems. The genetics of inherited neuropathy has significantly improved over the last decade and has increased the understanding of the normal biology of nerve tissue. The hereditary motor and sensory neuropathies (i.e., Charcot-Marie-Tooth neuropathies) are now better understood and represent a group of disorders with overlapping clinical characteristics but distinct pathology. Some can be identified by currently available commercial laboratory tests. Inherited disorders affecting only sensation (e.g., hereditary sensory neuropathy) are quite rare. They may involve either small fiber sensory loss (pain and temperature) or loss of larger sensory fibers (proprioception, vibration). Identifying the type of sensory loss on examination can help refine the differential diagnosis.

**Occupational Exposure**

Incidental exposure to agents that are toxic to nerve may be easily missed on a routine history and review of systems. Contact with solvents, glues, fertilizer, oils, and lubricants can result in a neuropathy that cannot be distinguished from other causes of idiopathic or hereditary etiology.

**Medications**

Injury to nerve caused by medications or vitamins is sometimes overlooked. Over-the-counter oral preparations can result in a predominantly sensory neuropathy (even at therapeutic doses). Patients with a neuropathy from some other cause may have an exacerbation of their symptoms when taking some over-the-counter medications (Table 5).

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Selected medications associated with a sensory or a sensory predominant neuropathy which should be avoided in patients with a pre-existing peripheral neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>chloramphenicol</td>
<td>metronidazole</td>
</tr>
<tr>
<td>cisplatin</td>
<td>nitrous oxide</td>
</tr>
<tr>
<td>ethambutol</td>
<td>nucleosides</td>
</tr>
<tr>
<td>glutethimide</td>
<td>didanosine</td>
</tr>
<tr>
<td>hydralazine</td>
<td>dideoxycytosine</td>
</tr>
<tr>
<td>isoniazid</td>
<td>stavudine</td>
</tr>
</tbody>
</table>

**EXAMINATION**

In addition to the body diagram, the physical examination can be helpful in localizing the site of injury. Evaluation of deep tendon reflexes examines both an afferent component to carry input from the muscle tendon to the spinal cord and an efferent component to produce a muscle twitch during a reflex. The reflex is affected by descending cortical-spinal inputs that mitigate or enhance the reflex arc. The arc reflects a specific root level and can be helpful in the localization of the process.

Pathology in the CNS is characterized by pathologically brisk reflexes and extensor plantar reflexes. Additionally there can be increased tone and spasticity. Pathology in the PNS would result in diminished or absent reflexes along with atrophy and/or reduced muscle tone. Asymmetric or absent reflexes suggest a focal neuropathy or radiculopathy. In a predominantly sensory neuropathy, the type of sensory loss can help indicate the nerve fibers involved (i.e., small fiber versus large fiber, or a mixed picture). The modalities of sensory loss which should be tested include those listed in Table 6.

<table>
<thead>
<tr>
<th>Table 6</th>
<th>Sensory modalities which should be included on a thorough examination and their anatomic correlates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modality</td>
<td>Fiber type (Periphery)</td>
</tr>
<tr>
<td>Light touch</td>
<td>small fiber</td>
</tr>
<tr>
<td>Temperature</td>
<td>small fiber</td>
</tr>
<tr>
<td>Pinprick</td>
<td>small fiber</td>
</tr>
<tr>
<td>2-point discrimination</td>
<td>small fiber</td>
</tr>
<tr>
<td>Proprioception</td>
<td>large fiber</td>
</tr>
<tr>
<td>Vibration</td>
<td>both small and large fiber</td>
</tr>
</tbody>
</table>

The most useful information from the sensory examination results from the distribution of the deficit (symmetric versus asymmetric) and the quality of the sensory loss.

Sensory loss and neuropathy frequently can be associated with systemic diseases such as diabetes and several connective tissue disorders. Clinical signs on the general examination can be helpful if there is evidence of multiple organ systems disorders. Autoimmune, inflammatory, metabolic, and neoplastic disease are some of the types of systemic illness which can present with peripheral nerve involvement resulting in numbness, paresthesia, and/or weakness. Careful attention to key clinical signs on general examination can result in the underlying disease as well as the etiology for the neuropathy.

**Evaluation: Work-Up**

One of the primary goals in patient work-up is to identify a treatable underlying process. Evaluation should include serologic and radiographic evaluation where appropriate to clarify the differential diagnosis and treatment plan (Table 7).

**CNS**

Sensory loss or numbness localized to the CNS is most typically associated with stroke or inflammatory disease. Evaluation of a patient with a suspected stroke, primarily involving sensation, should include screening risk factors such as hypertension, diabetes, cholesterol, tobacco use, and arrhythmia. An MRI of the brain is usually indicated. Ischemic or inflammatory disease thought to be localized to the spinal cord should be evaluated by an MRI.
and a lumbar puncture. The presence of elevated protein and an increased number of white blood cells in the cerebrospinal fluid suggests inflammation (myelitis). It is more difficult to define the specific etiology. Viral pathogens such as varicella, human T cell lymphotropic virus type 1, and human immunodeficiency virus have been demonstrated by high viral titers. Multiple sclerosis is a clinical diagnosis requiring multiple signs and symptoms at more than one point in time and MRI frequently can demonstrate plaques.

Electrodiagnosis

The evaluation of the functional health of peripheral nerves by nerve conduction studies (NCSs) and of affected muscles by needle electromyography (EMG) is often an essential component of the work-up. These tests can help localize nerve/muscle pathology and suggest an etiology. NCSs especially are helpful in identifying treatable causes of neuropathy by demonstrating primary demyelinating processes. Impairment of conduction velocity or evidence of conduction block in a focal region or in multiple regions can help define a demyelinating neuropathy. On the other hand, a reduced amplitude of the evoked response is more characteristic of an axonal neuropathy. It is important to note that axonal loss can be the result of a primary pathologic process attacking the axon or may be secondary to demyelination.

The EMG examination assesses the rate, amplitude, and frequency of electrical impulses being transmitted by the muscle. While NCSs can differentiate demyelinating versus axonal, the EMG is able to distinguish between the presence of denervation versus a primary muscle disease (myopathic process). The role of EMG in assessing a patient with only numbness is limited since it is only testing the motor nerves. However, a patient complaining of sensory loss in a radicular pattern may not be aware of any motor weakness (and the physical examination may be normal), but the EMG may demonstrate some motor axon involvement as the EMG can detect abnormalities with much greater sensitivity than the physical examination. It would take a 50% loss motor fibers to detect weakness on physical examination while a loss of only 5% can be detected by EMG. The added sensitivity in detecting abnormalities of motor units can implicate a combined motor-sensory etiology.

**BIBLIOGRAPHY**

Electrophysiologic Testing in Generalized Weakness

Insert

Jasper Daube, MD
Department of Neurology
Mayo College of Medicine
Rochester, Minnesota

GENERALIZED WEAKENSS CLINICAL CASE FINDINGS

Case 1 – 67-year-old woman with leg weakness

8-year history of slowly progressive, painless weakness

- 8 years ago - trouble arising from floor
- 4 years ago - trouble arising from chair
- 2 years ago - falls, give way of left leg

- Denies atrophy, fasciculations, muscle pain, sensory symptoms, or any upper extremity or trunk symptoms
- Previous needle electromyography (EMG) and nerve conduction studies (NCSs) normal

Clinical Examination: Uses upper extremities to arise from seated

- -2 weakness quadriceps with mild, bilateral atrophy
- -1 to -2 weakness left-right finger flexors and wrist flexors
- Remainder of neurologic examination is normal, including reflexes and sensory examination

NCS – normal peroneal, tibial, and sural

COMMENT

Scattered, myotonic discharges in multiple muscles

REPORT

Summary - NCSs are normal. Needle EMG shows fibrillation potentials and myotonic discharges with a mixture of short and long duration, polyphasic, rapidly recruited motor unit action potentials (MUAPs) in proximal and distal muscles.

Interpretation – The findings are those of a chronic, severe, diffuse myopathy. Fibrillation potentials in myopathic disorders may indicate the presence of necrosis, splitting, or vacuolization of muscle fibers. Mixed MUAPs can be seen in disorders that affect both nerve and muscle or in very chronic myopathies such as inclusion body myositis (IBM), chronic polymyositis or some muscular dystrophies. IBM is most likely with this combination of EMG and clinical findings.

MUSCLE BIOPSY – IBM

COMMENT

The distribution of weakness is an important clue to IBM. Mixed MUAP changes are also typical, but can be seen in very chronic myositis.

<table>
<thead>
<tr>
<th>EMG</th>
<th>Fibrillation</th>
<th>Recruit</th>
<th>Duration</th>
<th>Amplitude</th>
<th>Phases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biceps brachii</td>
<td>0</td>
<td>reduced</td>
<td>+ long +short</td>
<td>+low</td>
<td>25%</td>
</tr>
<tr>
<td>FDI</td>
<td>0</td>
<td></td>
<td>+long +short</td>
<td>+low</td>
<td>15%</td>
</tr>
<tr>
<td>FCR</td>
<td>++</td>
<td>reduced</td>
<td>+long +short</td>
<td>+low</td>
<td>25%</td>
</tr>
<tr>
<td>Medial gastroc.</td>
<td>+</td>
<td>reduced</td>
<td>+long +short</td>
<td>+high +low</td>
<td>25%</td>
</tr>
<tr>
<td>TA</td>
<td>+</td>
<td>reduced</td>
<td>+long</td>
<td>+high</td>
<td>15%</td>
</tr>
<tr>
<td>Vastus medialis</td>
<td>+</td>
<td>rapid</td>
<td>+short</td>
<td>+low</td>
<td>50%</td>
</tr>
<tr>
<td>TFL</td>
<td>+</td>
<td></td>
<td>+long</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraspinal</td>
<td>+</td>
<td></td>
<td>+long +short</td>
<td>+low</td>
<td>25%</td>
</tr>
</tbody>
</table>

EMG = electromyography; FCR = flexor carpi radialis; FDI = first dorsal interosseous; TA = tendon achilles; TFL = tensor fasciae latae
Case 2: 20-year-old college student 2 weeks progressive generalized weakness

Day 1.	Myalgia, headache, sore throat, fever
10. Student Health: penicillin for “strep throat”, persistent emesis
11. Emergency Room - Urinary retention, lethargy, unsteady
12. Diplopia, mild proximal weakness, brisk deep tendon reflex, bilateral Babinski
13. Reduced reflexes, progressive weakness, shortness of breath, tachycardia
14. Hospitalized: Head computed tomography and magnetic resonance imaging (MRI) normal; Cerebrospinal fluid (CSF) cells & protein increased

Diagnosis – Guillain–Barré with myelopathy, polyradiculoneuropathy, and autonomic neuropathy

Treatment Plan: Start 5 days intravenous immunoglobulin (IVIg)

Day 14

NCS

All motor amplitudes were low with no dispersion
Median motor and peroneal responses absent
No F waves
Conduction velocities and blink reflexes normal
Repetitive stimulation normal

EMG

Poor or no activation
Two muscles with reduced recruitment
No fibrillation potentials

REPORT

There has been marked progression of the disorder. There is now much clearer evidence of a widespread, demyelinating neuropathy with distal involvement that could account for the paralysis.

Day 23 IVIg 5 days - slow improvement; antibiotics continued
Day 60

NCS

NCSs reveal markedly reduced or absent compound muscle action potentials throughout with markedly slowed conduction velocities and prolonged distal latencies. There is an ulnar conduction block in the forearm on the left. The blink reflex was present, but markedly prolonged.

EMG

There are fibrillation potentials throughout, but with clear MUAP activation of normal or mildly long duration in the proximal upper limb.

REPORT

The findings are now those of a severe polyradiculopathy with prominent demyelination, as well as moderate axon loss. There has been improvement since the previous study. Fibrillation potentials are more prominent, but this reflects the Wallerian degeneration that has occurred, and does not indicate a worsening.

3 months – Reflexes return; tracheostomy and PEG out

6 months – Return to school with good limb strength

COMMENT

The distinction between an axonal motor neuropathy and an acute demyelinating neuropathy is not always easy. Every attempt should be made to define the diagnosis and stop specific therapy too soon.

Case 3: 65-year-old woman with fatigue

• 2 years of difficulty with household chores, “tired”
• Difficulty squatting at “Curves”s
• EMG 1 year ago – normal NCS and EMG
• Limited improvement on sertraline hydrochloride
• Examination - mild proximal weakness including difficulty swallowing. Normal reflexes, cranial nerves, sensation, and gait

NCS

Motor and sensory NCSs are normal in the arm and leg, including F-wave latencies. Slow repetitive stimulation of ulnar/hypothenar,
accessory/trapezius, and peroneal/anterior tibial muscles before and after exercise is normal.

**EMG**

Needle EMG showed short duration MUAPs in several proximal muscles, including the genioglossus. A few fibrillation potentials were seen in the thoracic paraspinals.

**REPORT**

The findings are those of a very proximal myopathy. The absence of many fibrillation potentials argues against, but does not exclude, an active inflammatory myopathy.

**BIOPSY**

Sarcoidosis

**COMMENT**

While the clinical and EMG picture make an inflammatory myopathy most likely, a muscle biopsy should always be considered to obtain a more definitive diagnosis. Sarcoidosis may present initially with muscle involvement.

**Case 4: 29-year-old woman with muscle aching**

- Healthy - 5 years muscle aching
- Mild elevations of creatine kinase (CK) (300 - 550)
- Examination normal
- Mild weakness, limited to left triceps

**NCS**

Motor and sensory NCSs normal in arm and leg. Normal repetitive stimulation.

**EMG**

Short duration MUAPs with mild, scattered fibrillation potentials in proximal muscles.

**REPORT**

The findings are mild, but consistent with a proximal myopathy, possibly inflammatory.

**BIOPSY**

Scattered, small, atrophic fibers with rare necrotic fibers. Consider myotonic dystrophy, Type 2.

**GENE TEST**

Myotonic dystrophy type 2 (DM2) showed CCTG repeat expansions (>12,100 bp). Confirmed in relatives.

**COMMENT**

Myotonic discharges in DM2 are more prominent proximal, predominantly wane, and may be few and far between.

**Case 5: 45 –year-old interior designer with 3 months generalized weakness**

- Brain stem astrocytoma-stable 2 yrs after radiation therapy
- Temporal lobe herpes simplex virus (HSV) encephalitis-better year after acyclovir
- Bulbar dysfunction from tumor-dexamethasone and temozolamide
- 2 mo progressive weakness with no other symptoms or signs
- CSF and EMG performed at home - axonal and demyelinating neuropathy
- Hospital transfer – flaccid quadriplegia with mild facial weakness and dyspnea
- Other cranial nerves, reflexes and sensation normal
- MRI 10 mm mass and residuals of HSV; with deep vein thrombosis

**EMG**

Short duration, polyphasic, stable MUAPs with rapid recruitment in all muscles. Scattered fibrillation potentials

**NCS**

CMAPs are low amplitude and markedly long duration without dispersion. F-wave latencies are normal, but F waves are small. Normal sensory NCSs. Normal repetitive stimulation.

**ADDITIONAL STUDIES**

Low amplitude MUAP with direct muscle stimulation. Normal motor unit number estimates.

**REPORT**

The findings are those of a severe, generalized myopathy of the type seen with critical illness. This pattern can occur with high dose steroid medication.

No evidence of an additional, neurogenic process or defect of neuromuscular transmission was found.

**FOLLOW-UP**

Full return of strength after 4 months

**COMMENT**

Critical illness myopathy can be difficult to distinguish from neuropathy. Prolonged CMAP without dispersion and small MUAPs are important distinguishing features.
Case 6: 64-year-old woman with 3 years progressive spastic dysarthria and dysphagia

- **History**
  - 1st year - normal EMG and head MRI
  - 2nd year – progressive bilateral leg weakness and slow walking – Diagnosis (Dx) – primary lateral sclerosis (PLS)
  - 3rd year – muscle cramps, dyspnea and pseudobulbar affect

- REFERED FOR POSSIBLE ALS

- **Neurologic examination:**
  - Moderate spastic/flaccid dysarthria
  - Poor cough with weak tongue but no atrophy
  - Mild proximal muscle weakness with increased tone throughout
  - Markedly hyperactive reflexes with bilateral Babinski
  - Mild distal sensory loss

- **Basic laboratory studies** - all normal

- **Motor and sensory NCSs** – normal in arm and leg

- **Needle EMG**– widespread fibrillation potentials with long duration, polyphasic MUAP in arm, leg and thoracic paraspinal muscles

Which of the following additional laboratory studies would you perform?
- CK
- Lyme titer
- Anti-GM1 antibody
- Glutamic acid decarboxylase (GAD)65 antibody
- Ceruloplasmin
- Spinal fluid
- Muscle biopsy
- MRI
- None

LABORATORY STUDIES ALL NORMAL EXCEPT

CK – 184 (< 176); Serum GAD 65 antibody-284 (<0.02); cerebral spinal fluid GAD65 antibody 0.49 (<0.2) = autoimmune disorder

SUBSEQUENT EVALUATION

Axial and neck rigidity. Normal startle testing

TREATMENT

Intravenous methylprednisolone (IVMP) 1 gram daily for 3 days followed by 4 weeks of pulse Rx. Maintained on monthly IVMP with azathioprine 75 twice daily.

No neurologic progression over the next 15 months with improved speech and swallowing.

REPEAT EMG 18 MONTHS

No fibrillation potentials anywhere. MUAP unchanged. NCS normal.

PLS is excluded by the prominent signs of denervation, making amyotrophic lateral sclerosis (ALS) highly likely. However the laboratory findings indicate a unique, autoimmune motor neuron disease. Other autoimmune disorders associated with markedly elevated GAD 65 antibodies have been misdiagnosed as multiple system atrophy, progressive supranuclear palsy, and myelopathy. Voltage gated potassium channel autoimmunity provides another example of immunotherpapy responsive neurologic disorders misdiagnosed as neurodegenerative. Autoimmune motor neuron disease should be suspected in atypical ALS-like syndromes (symmetry, long-time course, axial rigidity, limited atrophy, ataxia and hypothyroidism or other auto-immune disorders). A short trial of IVMP (over a 4-6 week period) may serve as a diagnostic tool regardless of serological or spinal fluid findings.
Dysimmune Neuropathies

Kenneth C. Gorson, MD
Benn E. Smith, MD
Ted M. Burns, MD
Richard A. Lewis, MD

2009 COURSE B
AANEM 56th Annual Meeting
San Diego, California
Dysimmune Neuropathies

Faculty

Ted M. Burns, MD
Associate Professor
Department of Neurology
University of Virginia
Charlottesville, Virginia

Dr. Burns is an associate professor of neurology at the University of Virginia in Charlottesville. He graduated from Kansas University Medical School and completed his neurology residency at the University of Virginia (UVA). He later completed 1-year fellowships in electromyography/neuromuscular diseases at UVA, and peripheral nerve diseases at the Mayo Clinic in Rochester, Minnesota. He is board certified in neurology, clinical neurophysiology, and electromyography. Dr. Burns is the director of the EMG laboratory at UVA, director of the UVA neurology residency program, and director of the UVA clinical neurophysiology fellowship program. He is the editor of the weekly podcast for Neurology. He is also the editor of the AANEM’s Nerve and Muscle Junction podcasts. He is a member of the AANEM’s Continuing Medical Education committee and a member of the American Board of Psychiatry and Neurology’s (ABPN) Neurology Clinical Neurophysiology committee, and the ABPN Neurology Recertification and Maintenance of Certification committee.

Kenneth C. Gorson, MD
Professor
Department of Neurology
St. Elizabeth’s Medical Center
Tufts University School of Medicine
Boston, Massachusetts

Dr. Gorson is professor of neurology in the Department of Neurology at St. Elizabeth’s Medical Center, Tufts University School of Medicine, in Boston, MA. Dr. Gorson has published over 60 original peer-reviewed research articles, book chapters, and reviews pertaining to Guillain-Barre’ syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), paraprotein-associated neuropathies, vasculitic neuropathy, and various other inflammatory and immune-mediated disorders of the peripheral nervous system. His clinical and research expertise extends to patients with neuropathies associated with diabetes, connective tissue disorders, and cancer, inherited peripheral neuropathies, and disorders of muscle, myasthenia gravis (MG), and amyotrophic lateral sclerosis. Dr. Gorson also has extensive expertise in the medical management of numerous chronic neuropathic and musculoskeletal pain disorders. He has been a principal investigator in several clinical research studies, including experimental treatment trials for CIDP, multifocal motor neuropathy, MG, diabetic neuropathy, painful neuropathies, and post-herpetic neuralgia. He has lectured widely to medical specialists and patient support groups on various topics in the field of neuromuscular diseases. Dr. Gorson is an active member of the American Academy of Neurology (AAN) and AANEM, and has previously served on the sub-committee responsible for the selection of neuromuscular courses for the annual meeting of the Academy. He also served as a councilor for the Neuromuscular Section for the AAN.

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Course Chair: Anthony E. Chiodo, MD

The ideas and opinions expressed in this publication are solely those of the specific authors and do not necessarily represent those of the AANEM.
Richard A. Lewis, MD
Professor and Associate Chair
Department of Neurology
Wayne State University School of Medicine
Detroit, Michigan

Dr. Lewis is professor and associate chair of neurology and co-director of the neuromuscular program at Wayne State University School of Medicine. He is also director of the clinical neurophysiology laboratory. He trained in neurology at the University of Pennsylvania and remained on the faculty there before taking positions at the University of Connecticut and Eastern Virginia Medical School. Dr. Lewis has been a member of the AANEM since 1979 and has been on a number of committees including the AANEM Examination and Education Committees. He has been a participant in practice parameter committees on conduction block, multifocal motor neuropathy, and peripheral neuropathy. He is deputy editor of the Journal of the Neurological Society and serves on multiple other editorial boards including Muscle & Nerve. He is on the national and international Medical Advisory Boards of the Myasthenia Gravis Association and Guillain-Barré Syndrome/Chronic Inflammatory Demyelinating Polyneuropathy Foundation International. Dr. Lewis’ interests include the clinical and electrophysiologic aspects of the demyelinating neuropathies, both acquired and inherited. He is probably best known for his paper on multifocal demyelinating neuropathy, a disorder that is now known as “The Lewis-Sumner Syndrome.”

Benn E. Smith, MD
Associate Professor of Neurology
Mayo Clinic College of Medicine
Mayo Clinic
Scottsdale, Arizona

Dr. Smith completed neurology residency training at the Mayo Clinic in Rochester in 1988. He completed an EMG Fellowship in 1989 and a peripheral nerve fellowship in 1990, also at the Mayo Clinic. Since 1990 he has been on the faculty of the Mayo Clinic College of Medicine at the Arizona campus where he has served as the EMG laboratory director and EMG/neuromuscular fellowship program director. His current research focus is on the development of novel noninvasive diagnostic modalities to investigate peripheral nerve and peripheral neuropathy including spinohalamic sensory pathways and cutaneous sensory receptors.
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Dysimmune Neuropathies

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OBJECTIVES After attending this session, participants will be able to (1) discuss the scope of immune-mediated disorders that affect the peripheral nerve, (2) discuss the appropriate classification of dysimmune neuropathies and the optimal diagnostic approach to them, (3) understand evidence-based treatment options, and (4) discuss the current research to better understand and treat these various disorders.

PREREQUISITE This course is designed as an educational opportunity for physicians.

ACCREDITATION STATEMENT The AANEM is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education (CME) for physicians.

CME CREDIT The AANEM designates this activity for a maximum of 3.25 AMA PRA Category 1 Credit(s).™ If purchased, the AANEM designates this activity for 2 AMA PRA Category 1 Credit(s).™ This educational event is approved as an Accredited Group Learning Activity under Section 1 of the Framework of Continuing Professional Development (CPD) options for the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada. Each physician should claim only those hours of credit he or she actually spent in the educational activity. CME for this course is available 10/09 - 10/12.
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<tr>
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<td>Philadelphia, Pennsylvania</td>
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<tr>
<td>Mazen M. Dimachkie, MD</td>
<td>Kansas City, Kansas</td>
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<tr>
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<td>David Bryan Shuster, MD</td>
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<td>Benjamin S. Warfel, II, MD</td>
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### 2008-2009 AANEM PRESIDENT

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<tr>
<th>Michael T. Andary, MD, MS</th>
<th>East Lansing, Michigan</th>
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INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired, immune-mediated condition affecting the peripheral nervous system.1-5,7 The pathogenesis of CIDP is incompletely understood and includes several humoral and cell-mediated mechanisms.7 Pathological studies have shown that there is endoneurial inflammation and nerve demyelination mediated by complement pathways and antibodies directed against antigenic components of the myelin sheath.4

The classic form of the disorder is characterized by: (1) progressive limb weakness, usually with a predilection for proximal muscles, sensory loss, and areflexia with a relapsing or progressive course; (2) electrophysiological features of demyelination, including prolonged distal motor and F-wave latencies, reduced conduction velocities, and conduction block and temporal dispersion; (3) laboratory features of albumino-cytological dissociation in the cerebrospinal fluid (CSF); and (4) inflammation, demyelination and remyelination on nerve biopsy.1-5,7,14 Increasingly the diagnosis can be confidently established by clinical and electromyography (EMG) criteria. Nerve biopsy is required less often, but can be helpful in selected cases.

Numerous clinical trials have established the short-term efficacy of immune therapies such as corticosteroids, plasma exchange (PE), and intravenous immune globulin (IVIg), making them the mainstays of treatment for CIDP. Several reports also indicate the promise of novel immune therapies.2,6,9,11-12,15 Although guidelines for the diagnosis and treatment of CIDP have been developed, the large variety of clinical and electrophysiological variants, associated systemic conditions, and lack of sustained improvement with standard treatments in up to a third of cases provide challenges to the clinician in practice.

This manuscript will focus on clinical features of CIDP, its clinical variants, concurrent diseases, including diabetes, and prognosis. It will also discuss laboratory evaluations, electrodiagnostic (EDX) criteria, the role of validated diagnostic criteria, pathology, differential diagnoses, treatment, alternative immunosuppressive regimens, and supportive therapies.

CLINICAL FEATURES

CIDP is one in a spectrum of acquired immune-mediated demyelinating neuropathies that differ from each other mainly in their time course and clinical features. The two traditional categories of acute inflammatory demyelinating polyneuropathy (AIDP) or Guillain-Barre’ syndrome (GBS) and CIDP have similar presentations, except the symptoms peak in less than 4 weeks in AIDP and are monophasic, while in CIDP, they progress for 8 weeks or more. For an illness that reaches its nadir between 4 and 8 weeks, the term subacute demyelinating neuropathy has been used.

The natural history of the latter group can follow the pattern of either AIDP (monophasic course with a plateau and then recovery) or CIDP (progressive or relapsing). In a large series, CIDP represented approximately 20% of initially undiagnosed neuropathies and accounted for approximately 10% of all patients referred to neuromuscular clinics.7 The disorder most commonly occurs in adults between 40 and 60 years, but can affect the elderly and children. There is a slight predilection for men.
The prevalence of CIDP is approximately 2 to 5 cases per 100,000 individuals, comparable to the frequency of AIDP. Two-thirds of cases are progressive, with the remainder relapsing. In the modern era, “relapses” often reflect treatment withdrawal (e.g., IVIg or rapid tapering of prednisone). They may also be triggered by infections or other systemic illnesses. Spontaneous relapses tend to affect younger individuals.

In its classic form, the initial symptoms of CIDP are progressive, symmetric limb weakness and sensory loss that usually begin in the legs. Patients report difficulty walking, climbing stairs, and arising from a chair. They may fall, or complain of reduced manual dexterity (e.g., trouble buttoning shirts, pulling up zippers) if hand weakness is present. A core clinical feature is proximal limb weakness, indicating a non-length-dependent neuropathy that implies proximal nerve demyelination and distinguishes such cases from the far more commonly encountered distal axonal polyneuropathies.

The majority of patients also have sensory features, with complaints of numbness, tingling, or buzzing of the acral extremities (paresthesias), and gait unsteadiness reflecting a sensory ataxia. Neuropathic pain is less common. The examination shows symmetric proximal and distal limb weakness, generalized hypo- or areflexia, and distal sensory loss with large fiber modalities (joint position, vibration) disproportionately affected.

Another useful clinical sign of CIDP in the early stages of the condition is the discrepancy between the degree of weakness and lack of atrophy in affected muscles; this strongly implicates nerve demyelination rather than axonal loss. Facial, oropharyngeal, and ocular involvement occur in less than 15% of patients, and autonomic dysfunction and ventilatory failure develop in fewer than 10% of cases. Unusual features associated with CIDP, mostly noted in case reports, include prominent vertigo, papilledema, and head drop.

**CLINICAL VARIANTS**

Several reports have highlighted a variety of unusual clinical patterns that probably represent variants of CIDP and are accepted under the same umbrella term because they share most of the clinical, electrophysiological, and cerebrospinal fluid findings (Table 1).9-10.14 Like AIDP, for example, certain forms may be classified as “functional” variants, with pure motor, pure sensory, and ataxic patterns. In several large series, up to 15% of patients had a pure sensory syndrome clinically. Many such cases have prominent demyelinating motor abnormalities on EMG studies, whereas others may simulate a ganglionopathy, with absent sensory potentials and normal motor studies. Nerve biopsy may be required to establish the diagnosis.

A rare but striking variant is a pure sensory, large fiber ataxic form manifest by inflammation and demyelination isolated to the sensory roots. Routine EDX studies are usually normal. Somatosensory evoked potentials demonstrate slowing at the level of the lumbar roots. The CSF protein level is elevated, and lumbar rootlet biopsy demonstrates characteristic pathological features of CIDP. This pattern has been termed chronic inflammatory sensory polyradiculopathy (CISP). The converse of this pattern, a generalized, pure motor demyelinating neuropathy, can be distinguished from multifocal motor neuropathy (MMN) by the presence of widespread proximal and distal limb weakness, relative symmetry, and response to corticosteroids.

In contrast, a number of "regional" variants have also been recognized, including the multifocal forms that simulate mononeuritis multiplex (Lewis-Sumner syndrome [L-SS] and multifocal acquired demyelinating sensory and motor neuropathy).10 These are purely upper limb demyelinating neuropathies that may be strikingly focal. A paraparetic form is associated with regional leg weakness and sensory loss, nerve root hypertrophy on magnetic resonance imaging (MRI) studies, and symptoms emulating a progressive cauda equina syndrome. A few patients have prominent or isolated cranial nerve palsies.

Experts have also identified a predominantly sensory demyelinating polyneuropathy that is rare, distal, and symmetric. Distal acquired demyelinating symmetrical neuropathy14 is quite similar to the polyneuropathy associated with an IgM monoclonal protein and elevated anti-myelin associated glycoprotein antibodies. This variant simulates a distal axonopathy and can be missed without careful EDX evaluation, especially if an M-protein is not present.

Other similar illnesses have been distinguished from typical CIDP based on temporal course or severity of the disorder. For example, investigators have identified patients with a time course between AIDP and CIDP. Occasionally, the initial manifestations of CIDP

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<td>Ataxic CIDP</td>
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<td>CISP</td>
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CIDP = chronic inflammatory demyelinating polyneuropathy; CISP = chronic inflammatory sensory polyradiculopathy; DADS = distal acquired demyelinating symmetric neuropathy; L-SS = Lewis-Sumner Syndrome; MADSAM = multifocal acquired demyelinating sensory and motor neuropathy.
may mimic the acute onset of GBS followed by slower progression, or with a chronic, relapsing course. Such cases may be reclassified as CIDP only after 3 or more relapses or progression beyond 9 weeks. Rare forms of CIDP include those with mild distal paresthesias, demyelinating NCSs, and an elevated CSF level. Termed “minimal CIDP” to reflect the limited nature of the illnesses, these regional and functional variants seem to respond to the conventional therapies for CIDP with about the same frequency, but have never been carefully subjected to controlled study.

CIDP AND CONCURRENT DISEASES

A number of medical conditions occur simultaneously with CIDP and are implicated in its pathogenesis. Most large series of CIDP, for example, show that approximately 15-20% of patients have a monoclonal gammopathy detected by serum immunofixation. Some of these patients have a malignant plasma cell dyscrasia (multiple myeloma, polyneuropathy, organomegaly, endocrinopathy, M-spike, skin changes [POEMS] syndrome, lymphoma, or Waldenström's macroglobulinemia), but the majority have a monoclonal gammopathy of undetermined significance (MGUS).

These patients are generally managed no differently than those with classical CIDP once a plasma cell disorder has been excluded. In most of those who have CIDP-MGUS and an immunoglobulin G (IgG) or IgA monoclonal protein, their disorder is indistinguishable from idiopathic CIDP, including improvement with immune therapies. In contrast, those with IgM-MGUS usually have greater sensory loss, tremor, more severe distal demyelinating abnormalities on EMG studies, increased frequency of anti-myelin associated glycoprotein (anti-MAG) or other pathogenic anti-neuronal antibodies, and are less responsive to standard treatments for CIDP.

Approximately 10-15% of patients with CIDP have an associated systemic medical disorder, although the precise relationship of the underlying illness to the neuropathy varies from case to case (Table 2). In essence, these cases may reflect “secondary symptomatic” inflammatory demyelinating neuropathies, as distinguished from the idiopathic variety. These include several autoimmune or connective tissue disorders (systemic lupus erythematosus, thyroid disease, rheumatoid arthritis, glomerulonephritis, Sjögren syndrome, myasthenia gravis, and sarcoidosis). Other conditions associated with CIDP include chronic infections (human immunodeficiency virus [HIV], human T-cell lymphotropic virus type 1 [HTLV I], hepatitis B and C); organ transplantation; various malignancies; diabetes mellitus; and renal insufficiency. CIDP can also be superimposed on a hereditary neuropathy or associated with multiple sclerosis.

It is not known if one of these concurrent illnesses alters the response to therapy or the prognosis of patients with CIDP. However, identifying these associated conditions may facilitate the initial choice of therapy (e.g., corticosteroids in patients with CIDP and systemic lupus erythematosus). It certainly has important implications for the patient (e.g., CIDP associated with HIV infection or lymphoma).

In many cases of acquired demyelinating polyneuropathy associated with systemic illness, the pathophysiology of the nerve damage may differ from idiopathic CIDP, but the clinical and electrophysiological features often overlap. CIDP may also be associated with

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<th>Table 2: Concurrent diseases associated with inflammatory demyelinating polyneuropathy (“secondary” CIDP)</th>
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**Chronic Infections**
- HIV infection
- HTLV I
- Lyme disease
- Cat scratch disease
- Epstein-Barr infection
- Hepatitis C

**Medications**
- Interferon alpha
- Procainamide
- Tacrolimus

**Connective tissue and auto-immune disorders**
- Systemic lupus erythematosus
- Sjögren syndrome
- Rheumatoid disease
- Giant cell arteritis
- Inflammatory bowel disease
- Myasthenia Gravis
- Chronic active hepatitis
- Multiple sclerosis

**Vaccinations**
- Solid organ transplantation
- Hereditary neuropathy (CIDP and CMT)

**Systemic Medical Disorders**
- Diabetes Mellitus
- Thyrotoxicosis
- Chronic renal failure requiring dialysis
- Membranous glomerulonephropathy

**Malignancy**
- Hepatocellular carcinoma
- Melanoma
- Pancreatic carcinoma
- Colon adenocarcinoma
- Lymphoma
- Paraneoplastic demyelinating neuropathy

**Paraprotein associated disorders**
- Monoclonal gammopathy of undetermined significance (MGUS)
- Osteosclerotic myeloma (POEMS syndrome)
- Multiple myeloma
- Waldenström's macroglobulinemia
- Amyloidosis
- Castleman's disease

CIDP = chronic inflammatory demyelinating polyneuropathy; CMT = Charcot-Marie-Tooth disease; HIV = human immunodeficiency virus; HTLV I = human T-cell lymphotropic virus type 1; POEMS = Polyneuropathy, Organomegaly, Endocrinopathy, monoclonal gammopathies, Skin changes.
medications (procainamide, interferon alpha) or any number of vaccinations (although a relationship between CIDP and a specific vaccine has never been established).

CIDP and DIABETES MELLITUS

Patients with diabetes mellitus and a polyneuropathy frequently have elements of demyelination on EMG studies, and many have an elevated CSF protein level. Furthermore, nerve biopsy may reveal modest demyelinating changes and even inflammatory cell infiltration. Irrespective of a diagnosis of concurrent diabetes mellitus and a distal, symmetric sensory polyneuropathy, most experts attribute the illness to CIDP if the clinical and laboratory features (EMG and spinal fluid studies) support the diagnosis. This is predicated on the fact that most patients with a distal diabetic polyneuropathy lack proximal or generalized weakness, a progressive course over a few months, conduction block (at sites not prone to entrapment), or other widespread unequivocal demyelinating features on EMG studies.

The possibility that diabetic patients are more predisposed to developing CIDP has yet to be established by rigorous epidemiological studies, and remains controversial. In uncertain cases, a therapeutic trial of IVIg or PE is warranted. In a patient with diabetes, a substantial and rapid objective clinical improvement supports a diagnosis of CIDP.

LABORATORY EVALUATION

The laboratory tests indicated for suspected CIDP patients include: complete blood count, serum chemistries, blood urea nitrogen, creatinine, HIV titer, fasting blood glucose and glycosylated hemoglobin, anti-nuclear antibodies, and most importantly, serum and urine immunofixation electrophoresis to exclude a monoclonal protein. The detection of a monoclonal protein warrants investigation for a malignant plasma cell dyscrasia before concluding that the M-spike represents MGUS. An M-protein level greater than 3 g/dl is virtually always indicative of a malignant plasma cell dyscrasia. A level less than 1.5 g/dl is more often observed in younger patients or the POEMS syndrome associated with Castleman’s disease.

Additional laboratory studies that may be indicated in certain cases that suggest a connective tissue or chronic infectious disorder include: serum antineutrophil cytoplasmic antibodies level; rheumatoid factor; angiotensin converting enzyme; anti-SSA/SSB antibodies; and hepatitis B and C, HTLV I, HIV and Lyme serologies. For patients suspected of having an inherited neuropathy and in young patients with only slowed conduction velocities on EDX studies, genetic studies for Charcot-Marie-Tooth (CMT) disease types IA, IB, and X can exclude these conditions. Brain and spinal cord MRI studies should also be obtained when the neurological history or findings suggest concomitant central nervous system demyelination. In those individuals with constitutional features (e.g., unexplained weight loss, fevers, adenopathy, anemia), a search for a malignancy is warranted.

A lumbar puncture is also indicated in patients suspected of having CIDP. An elevated CSF protein level (> 45 mg/dl) is detected in at least 80% of patients. However, the diagnosis of CIDP should not be excluded based only upon a normal CSF protein concentration. The cell count is usually normal, but as many 10% of patients have greater than 5 lymphocytes/mm.3 The American Academy of Neurology (AAN) criteria indicate that there should be fewer than 10 cells in the spinal fluid, and fewer than 50 in patients with HIV infection.3 Accordingly, the presence of a CSF pleocytosis should prompt an evaluation for HIV infection as well as Lyme disease, lymphomatous meningitis, and sarcoidosis. Oligoclonal bands are found in the CSF in approximately 65% of cases and do not appear to be of any consequence.

EDX CRITERIA

Nerve conduction studies (NCSs) establish the diagnosis of CIDP with confidence in the majority of cases. Several EDX criteria have been proposed. All require some combination of: (1) reduced conduction velocities (CV), i.e., < 80% of the lower limit of normal (LLN) if the distal motor amplitude is normal, and < 70% of LLN if the amplitude is substantially reduced; (2) prolonged distal motor latencies; (3) prolonged F wave latencies, i.e., > 125% of the upper limit of normal (ULN) if the distal motor amplitude is normal, and > 150% of ULN if the amplitude is reduced for distal latencies and F waves; and (4) conduction block (CB)/temporal dispersion (TB), i.e., CB is > 50% reduction of proximal/distal (p/d) amplitude and abnormal TD is > 130% increase of p/d duration.3

According to the AAN criteria, the presence of three of the four criteria in two or more nerves establishes the electrophysiological diagnosis of CIDP for research purposes.3 For the practicing clinician, these various schemes are contrived since only 50-60% of patients with typical clinical features of CIDP fulfill these strict EDX criteria. Accordingly, over the last 15 years at least 10 alternative EMG criteria have been proposed, with varying degrees of greater sensitivity without sacrificing specificity (Table 3). None, however, have been validated in a rigorous manner, thus contributing to further controversy and confusion.1-3,5,9,13-14
Because demyelination in CIDP is frequently a multifocal process, study of multiple nerves (at least four and probably more) is necessary. Similarly, proximal nerve and root stimulation may be required in some cases to confirm proximal CB when this finding is not detected in distal segments. Care must be taken to ensure that nerve stimulation is supramaximal.

Computer simulation studies have demonstrated that up to a 50% amplitude reduction between proximal and distal points of stimulation may occur in normal motor nerves. This phenomenon is termed "pseudo-conduction block," and is attributed to interphase cancellation of motor potential waveforms. Therefore, the criterion for definite CB has been increased from 20% (initial AAN criteria) to 50% amplitude reduction following proximal nerve stimulation, especially with studies of very proximal nerve or root segments.

Abnormalities of the sensory nerve action potentials (SNAPs) have not been addressed in any of the published EMG criteria for CIDP. Most CIDP patients have low or absent SNAPs. When sensory potentials can be obtained, the distal latencies or conduction velocities are usually slowed and in the demyelinating range. A characteristic finding of absent or reduced median or ulnar SNAPs with normal sural sensory potentials ("sural sparing") indicates a

<table>
<thead>
<tr>
<th>Table 3 Proposed Published Electrodiagnostic Criteria for CIDP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Set 1: AAN Ad hoc subcommittee; 3 of 4 criteria must be fulfilled</strong></td>
</tr>
<tr>
<td>1. Reduction in motor nerve conduction velocity (MNCV) in two or more nerves:</td>
</tr>
<tr>
<td>a. &lt;80% of lower limit of normal (LLN) if amplitude &gt;80% of LLN</td>
</tr>
<tr>
<td>b. &lt;70% of LLN if amplitude is &lt;80% of LLN</td>
</tr>
<tr>
<td>2. Partial conduction block (CB) in one or more motor nerves defined as &lt;15% change in duration between proximal and distal sites and &gt;20% drop in negative peak (−p) amplitude between proximal and distal sites.</td>
</tr>
<tr>
<td>3. Prolonged distal latencies (DML) in two or more nerves:</td>
</tr>
<tr>
<td>a. &gt;125% of upper limit or normal (ULN) if amplitude is &gt;80% of LLN</td>
</tr>
<tr>
<td>b. &gt;150% of ULN if amplitude is &lt;80% of LLN</td>
</tr>
<tr>
<td>4. Absent F-waves or prolonged minimum F-wave latencies in two or more motor nerves:</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 amplitude &lt;80% of LLN</td>
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</table>

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<thead>
<tr>
<th><strong>Set 2: Albers and Kelly; 3 of 4 criteria must be fulfilled</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Reduced MNCV in 2 or more nerves: &lt;75% of LLN</td>
</tr>
<tr>
<td>2. Prolonged DML in 2 or more nerves: &gt;130% of ULN</td>
</tr>
<tr>
<td>3. Partial conduction block (CB) or abnormal temporal dispersion in 1 or more nerves: &gt;30% drop in amplitude between proximal and distal sites</td>
</tr>
<tr>
<td>4. Prolonged F-wave latency in 1 or more nerves: &gt;130% of ULN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Set 3: Bromberg et al.; 3 of 4 criteria must be fulfilled</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Reduced MNCV in 1 or more nerves: &lt;70% of LLN</td>
</tr>
<tr>
<td>2. Prolonged DML in 2 or more nerves: &gt;130% of ULN</td>
</tr>
<tr>
<td>3. Partial conduction block (CB) or abnormal temporal dispersion in 1 or more nerves: &gt;30% drop in amplitude between proximal and distal sites</td>
</tr>
<tr>
<td>4. Prolonged F-wave latency in 1 or more nerves: &gt;130% of ULN</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th><strong>Set 4: Saperstein et al.; 2 of 4 criteria must be fulfilled</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Partial conduction block (CB) in one or more motor nerves defined as &gt;50% drop in negative peak amplitude between proximal and distal sites for median and ulnar nerves and &gt;60% drop in negative peak amplitude between proximal and distal sites for tibial and peroneal nerves.</td>
</tr>
<tr>
<td>2. Reduction in conduction velocity (MNCV) in two or more nerves:</td>
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<table>
<thead>
<tr>
<th><strong>Set 4: 2 of 4 criteria must be fulfilled (continued)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. &lt;80% of lower limit of normal (LLN) if amplitude &gt;80% of LLN</td>
</tr>
<tr>
<td>2. &lt;70% of LLN if amplitude is &lt;80% of LLN</td>
</tr>
<tr>
<td>3. Prolonged DML in 2 or more nerves:</td>
</tr>
<tr>
<td>a. &gt;125% of ULN if amplitude is &gt;80% of LLN</td>
</tr>
<tr>
<td>b. &gt;150% of ULN if amplitude is &lt;80% of LLN</td>
</tr>
<tr>
<td>4. Absent F-waves or prolonged minimum F-wave latencies in two or more motor nerves:</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 amplitude &lt;80% of LLN</td>
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<thead>
<tr>
<th><strong>Set 5: Inflammatory Neuropathy Cause and Treatment (INCAT) group diagnostic criteria</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Partial conduction block or abnormal temporal dispersion of conduction must be present in at least 2 nerves, and there must be significantly reduced conduction velocity, or significantly prolonged distal motor latency, or absent or significantly prolonged minimum F-wave latency in at least 1 other nerve. or,</td>
</tr>
<tr>
<td>2. In the absence of block or dispersion, significantly reduced conduction velocity, or significantly prolonged distal motor latency, or absent or significantly prolonged minimum F-wave latency must be present in at least 3 nerves, or,</td>
</tr>
<tr>
<td>3. In the presence of significant neuropathologic abnormalities in only 2 nerves, unequivocal histological evidence of demyelinated nerve fibers in a nerve biopsy must also be present</td>
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<tr>
<th><strong>Set 6: Nicolas et al. Electrodiagnostic Criteria for CIDP</strong></th>
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</thead>
<tbody>
<tr>
<td>1. CB/TD must be present in at least 3 different nerves with abnormal conduction values suggestive of demyelination in at least 1 nerve (including one of the nerves with CB/TD).</td>
</tr>
<tr>
<td>2. CB/TD must be present in 2 different nerves and abnormal conduction values in at least 1 other nerve.</td>
</tr>
<tr>
<td>3. CB/TD must be present in 1 nerve and abnormal conduction values in at least 2 other nerves.</td>
</tr>
<tr>
<td>4. No CB/TD, but abnormal conduction values must be present in 3 different nerves</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Set 7: Barohn et al. Electrodiagnostic Criteria for CIDP</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Reduction of motor nerve conduction velocities in 2 or more nerves &lt; 70% of the lower limit of the normal (LLN)</td>
</tr>
</tbody>
</table>
nonlength dependent pattern that suggests a demyelinating neuropathy. In contrast, the SNAPs are invariably normal in those with the CISP variant, as the pathology is found at the level of the sensory roots.

Needle electrode examination in those with a pure demyelinating form of CIDP shows reduced recruitment patterns of motor units without active or chronic denervation. The presence of abnormal spontaneous activity (fibrillation potentials) or large amplitude, long duration motor unit action potentials (MUAPs) indicates chronic partial denervation; reinnervation signifies an axonal component. These axonal changes are present in varying degrees in approximately 67% of cases.

EDX studies have several important shortcomings in establishing the diagnosis of CIDP: (1) patients may accrue substantial axonal loss with absent or greatly reduced MUAPs, and therefore, nerve conduction abnormalities may not fulfill criteria for demyelination; (2) those with a pure sensory variant may have absent SNAPs and relatively normal motor potentials; (3) a few patients have EDX abnormalities limited to proximal motor nerve segments that are detected only with motor root or Erb’s point stimulation; and (4) in clinical practice, there are a large group of patients without axon loss who do not fulfill any of the proposed EMG criteria and yet may still benefit from treatment. In these patients, spinal fluid analysis and nerve biopsy may be especially helpful to confirm the diagnosis. In those who do not fulfill strict EDX criteria, a therapeutic trial may be warranted.

### Table 3 (Continued) Proposed Published Electrodiagnostic Criteria for CIDP

<table>
<thead>
<tr>
<th>Set 8: European Federation of Neurological Societies (EFNS)/Peripheral Nerve Society Guideline Electrodiagnostic Criteria</th>
</tr>
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<tbody>
<tr>
<td><strong>Set 10: Magda et al. Electrodiagnostic Criteria</strong></td>
</tr>
<tr>
<td>Abnormalities in at least 3 nerves with at least 1 from category A or B</td>
</tr>
<tr>
<td>Category A* (demyelinating-range abnormalities)</td>
</tr>
<tr>
<td>F-wave minimal latency</td>
</tr>
<tr>
<td>120% ULN if CMAP _80% LLN</td>
</tr>
<tr>
<td>150% ULN if CMAP _80% LLN</td>
</tr>
<tr>
<td>Tibial H-reflex minimal latency 120% ULN</td>
</tr>
<tr>
<td>Conduction velocity</td>
</tr>
<tr>
<td>80% LLN if CMAP _80% LLN</td>
</tr>
<tr>
<td>70% LLN if CMAP _80% LLN</td>
</tr>
<tr>
<td>Distal Latency</td>
</tr>
<tr>
<td>125% ULN if CMAP _80% LLN</td>
</tr>
<tr>
<td>150% ULN if CMAP _80% LLN</td>
</tr>
<tr>
<td>Distal CMAP duration &gt; 9 ms</td>
</tr>
<tr>
<td>Proximal CMAP Temporal dispersion &gt; 30% (median, ulnar, or peroneal nerve)</td>
</tr>
<tr>
<td>Absent F waves with CMAP amplitudes &gt; 75% LLN (median or ulnar)</td>
</tr>
<tr>
<td><strong>Category B (possible partial conduction block)</strong></td>
</tr>
<tr>
<td>Proximal-distal CMAP amplitude decline of &gt; 30% (median nerve wrist–elbow, ulnar nerve wrist–below elbow, or peroneal nerve ankle–fibular head segments)†</td>
</tr>
<tr>
<td><strong>Category C (other abnormalities)</strong></td>
</tr>
<tr>
<td>CMAP amplitude, DL, CV, F-wave or H-reflex minimal latency abnormalities not meeting category A or B definitions</td>
</tr>
</tbody>
</table>

**Set 9: Thaisetthawatkul et al. Electrodiagnostic criteria**

Distal CMAP duration > 9 msec in 1 or more of 4 motor nerves.
THE ROLE OF VALIDATED DIAGNOSTIC CRITERIA

Due to a lack of consensus regarding the “best” diagnostic criteria for CIDP, an expert committee was convened under the auspices of the Medical Advisory Board of the Guillain-Barré Syndrome / Chronic Inflammatory Demyelinating Polynomalopathy Foundation International. The CIDP Criteria Working Group included 13 neurovascular neurologists from the United States, Canada, and Europe, an epidemiologist, and a biostatistician. In the first step, Koski and colleagues generated a set of candidate variables to be evaluated as potential diagnostic criteria based upon published literature and clinical expertise that could plausibly be expected to distinguish CIDP from other polyneuropathies. The selected candidate variables included aspects of the history, neurologic examination, EDX data, and ancillary laboratory studies.

The second step entailed detailed case descriptions, including the initial evaluation, EMG studies, laboratory data, CSF examination, genetic tests, and nerve biopsy information. These were submitted on 267 patients with CIDP, chronic acquired demyelinating neuropathies, such as LSS, paraprotein associated neuropathies, MMN, and “other” neuropathies (e.g., diabetes mellitus, toxic and familial neuropathies). A consensus diagnosis was established for each case when 11 or more of 15 expert reviewers agreed on the case classification (this consensus was defined as the “gold standard”). Information on candidate variables was abstracted from the case descriptions (Figure 1).9

Cases with consensus were divided into a “derivation sample” used to derive the classification rule, and a “validation sample” used to validate it. Validation of a classification rule in a second sample is important because a more accurate estimate of a rule’s performance is obtained when it is applied to a separate sample. To derive the rule, a classification and regression tree statistical approach was used. This involved considering all possible partitions of the cases based on all candidate variables to identify the partition that best distinguished between CIDP and non-CIDP cases. Once we made an initial partition, the process was performed repeatedly in resulting subgroups to identify groups of patients that are relatively homogeneous with respect to CIDP status. The derived diagnostic rule is shown in Figure 2.

In a patient with a chronic polyneuropathy progressive for more than 8 weeks, without a serum paraprotein or a genetic neuropathy, the diagnosis of CIDP would require one of the following: (1) in at least 75% of the motor nerves studied electrophysiologically—a recordable compound muscle action potential and either an abnormal distal latency in > 50% of nerves, or an abnormal motor CV in > 50% of nerves, or an abnormal F-wave latency in > 50% of nerves; OR 2) a symmetrical onset of motor symptoms and symmetrical weakness of all four limbs, with proximal weakness in at least one limb.

The sensitivity for these diagnostic criteria (Koski and colleagues) was 83%; the specificity 97% (Table 4). Importantly, the Koski criteria had much greater sensitivity when compared to several previously published criteria listed above (Table 5). The Koski criteria are best applied when an odd number of nerves are studied by EMG, and nerves that are likely to be absent (based on clinical assessment) are not sampled.

Figure 1 Development of validated diagnostic criteria for CIDP. CADP = chronic acquired demyelinating polyneuropathies; CIDP = chronic inflammatory demyelinating polyneuropathy

Figure 2 Criteria for classification of patients with CIDP

AAN = American Academy of Neurology; CIDP = chronic inflammatory demyelinating polyneuropathy
suspected CIDP, while others have shown that the procedure adds little if other clinical and EDX features support the diagnosis. One study, not surprisingly, has suggested that the presence of axonal loss on nerve biopsy implies a less favorable response to treatment.

DIFFERENTIAL DIAGNOSES

Several chronic demyelinating neuropathies may simulate CIDP and should be excluded before considering treatment. In many cases, non-CIDP forms of acquired demyelinating neuropathy may also be immune-mediated. Therefore, some of the treatments may overlap with therapies for CIDP. However, important distinctions exist (e.g., the lack of response to corticosteroids in patients MMN and anti-MAG neuropathy). In patients younger than 40 years, it is prudent to use deoxyribonucleic acid analysis to exclude hereditary demyelinating neuropathy (CMT1A, CMT1B, and CMTX) and hereditary neuropathy with liability to pressure palsies.

The latter disorders usually manifest in adolescence or young adulthood, and most patients have a positive family history and slower progression than CIDP. High arches, hammer toes, and palpably enlarged nerves are characteristic findings on examination. In contrast to CIDP, there is usually uniform conduction slowing in patients with CMT and generally no CB or TD. However, adding further to diagnostic confusion, several recent studies have demonstrated the presence of CB in patients with connexin 32 mutations associated with CMTX.

Acquired demyelinating neuropathies that should be distinguished from CIDP include IgM-MGUS associated neuropathies with anti-myelin associated glycoprotein (MAG) or anti-GD1b antibodies, as noted previously. Many experts have stressed that in IgM-MGUS neuropathy, the differences in the clinical presentation (distal, predominantly sensory pattern), electrophysiological features (distal demyelination, CB is less common), and lack of response to certain therapies (e.g., corticosteroids) warrant a distinction from idiopathic CIDP. For example, most patients with IgM-MGUS neuropathies, especially with elevated anti-MAG antibodies, have a chronic, slowly progressive and indolent course, and substantially prolonged distal motor latencies.

A randomized controlled trial demonstrated statistically significant and clinically meaningful efficacy of rituximab in this particular condition. Because this trial provided the highest level of evidence (Class I) for patients with IgM-MGUS neuropathy and elevated anti-MAG antibodies, rituximab should now be considered the initial treatment of choice in these cases, despite its off-label indication.

Similarly, MMN is an entity that should be distinguished from CIDP due to the focal or multifocal pattern, upper limb predominance, restricted involvement of motor fibers, and general lack of response to corticosteroids. Although intravenous immunoglobulin (IVIg) is an effective therapy for the majority of patients with CIDP and MMN, cyclophosphamide is the preferred second line therapy in MMN patients who do not respond to IVIg. Currently, a large, randomized, controlled trial to demonstrate efficacy of IVIg in MMN is underway.

### PATHOLOGY

The classic pathological features of CIDP include demyelination, remyelination (onion bulbs), endoneurial edema, and inflammatory cell infiltrates in the epineurium and endoneurium, usually with preferential involvement of the nerve roots. Chronically demyelinated and remyelinated nerve fibers form onion bulbs, identical to but less numerous than in hereditary demyelinating polyneuropathy (e.g., CMT disease type I). Routine toluidine blue, semi-thin plastic sections typically show an excess of large, thinly myelinated nerve fibers usually associated with varying degrees of acute axonal degeneration and reduced axonal density. Because CIDP is a multifocal process, nerve biopsy often does not yield a confirmatory diagnosis. Recent large series have demonstrated inflammatory changes in 10-50% of specimens, features of only axonal degeneration in 20-40%, and normal biopsies in approximately 20% of cases.

Inflammatory infiltrates are composed primarily of CD8+ and CD4+ lymphocytes and macrophages within the endoneurium. Analysis of teased fibers is probably the most sensitive method of demonstrating demyelinating changes, which are found in 50-80% of nerve biopsy specimens. However, the procedure is cumbersome and time-consuming and is performed primarily at specialized centers. This may be a problem for some clinicians due to limited regional availability. The utility of nerve biopsy in CIDP continues to engender controversy. Many experts endorse the value of routine nerve biopsy and teased fiber studies, in particular, in patients with suspected CIDP, while others have shown that the procedure adds little if other clinical and EDX features support the diagnosis. One study, not surprisingly, has suggested that the presence of axonal loss on nerve biopsy implies a less favorable response to treatment.

DIFFERENTIAL DIAGNOSES

Several chronic demyelinating neuropathies may simulate CIDP and should be excluded before considering treatment. In many cases, non-CIDP forms of acquired demyelinating neuropathy may also be immune-mediated. Therefore, some of the treatments may overlap with therapies for CIDP. However, important distinctions exist (e.g., the lack of response to corticosteroids in patients MMN and anti-MAG neuropathy). In patients younger than 40 years, it is prudent to use deoxyribonucleic acid analysis to exclude hereditary demyelinating neuropathy (CMT1A, CMT1B, and CMTX) and hereditary neuropathy with liability to pressure palsies.

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### Table 4 Sensitivity and specificity of the proposed rule in the derivation and validation samples

<table>
<thead>
<tr>
<th>Sample</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derivation sample (n=150)</td>
<td>56/58 (96%)</td>
<td>87/92 (95%)</td>
</tr>
<tr>
<td>Validation sample (n=117)</td>
<td>40/48 (83%)</td>
<td>67/69 (97%)</td>
</tr>
</tbody>
</table>

*Sensitivity: Among cases that were chronic inflammatory demyelinating polyneuropathy (CIDP) by consensus diagnosis, proportion that were classified as CIDP by proposed rule

**Specificity: Among cases that were non-CIDP by consensus diagnosis, proportion that were classified as non-CIDP by proposed rule

### Table 5 Sensitivity and specificity of previously published diagnostic criteria, as applied to the Koski et al. cohort (n=267)

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barohn et al., 1988</td>
<td>27%</td>
<td>94%</td>
</tr>
<tr>
<td>AAN Ad Hoc</td>
<td>11%</td>
<td>98%</td>
</tr>
<tr>
<td>Subcommittee, 1991</td>
<td>64%</td>
<td>75%</td>
</tr>
<tr>
<td>INCAT 2001</td>
<td>34%</td>
<td>99%</td>
</tr>
<tr>
<td>EFNS (2005)</td>
<td>58/71 (82%)</td>
<td>40/48 (83%)</td>
</tr>
</tbody>
</table>

AAN = American Academy of Neurology; CIDP = chronic inflammatory demyelinating polyneuropathy; EFNS = European Federation of Neurological Societies; INCAT = the Rotterdam Inflammatory Neuropathy Cause and Treatment Group.
Other diagnostic considerations that should be ruled out include toxin and medication-induced demyelinating neuropathies (e.g., solvents [glue-sniffing neuropathy], arsenic poisoning, amiodarone). A recent case report of some interest also indicated that Lyme disease caused a CIDP-like illness that responded to antibiotics.

**TREATMENT**

The primary goal of treatment is to reduce symptoms (weakness, sensory loss, imbalance and pain), improve functional status, and if possible, maintain long-term remission in patients with CIDP. Conventional therapy has included corticosteroids, PE, and intravenous infusion of IVIg (Table 6).

Improvement can be expected in 60-80% of patients with one of the standard treatments (steroids, IVIg, PE). Each of these has proven superior to placebo in randomized, double-blind, placebo-controlled studies. Accordingly, insurance reimbursement in the United States should no longer be a problem. Furthermore, randomized, prospective clinical trials have shown that PE and IVIg, and IVIg and prednisolone, have similar short-term efficacy.

The practical issues associated with these agents are the lack of a durable response in many patients and the difficulties of using ideally short-term therapies for long-term management of a chronic disease. IVIg is expensive, time-consuming, and may have limited availability. PE can be invasive for those who require central venous catheters, and requires well-trained personnel at specialized centers. Corticosteroids have a large number of potentially serious side effects and are often poorly tolerated when used as a long-term therapy.

**Prednisone**

There are numerous anecdotal reports demonstrating the efficacy of prednisone in CIDP, with response rates ranging from 40-95%. In a 3-month, randomized, placebo-controlled trial of alternate-day, high-dose prednisone (120 mg) in 28 patients, corticosteroids were found to be more effective than placebo. The effect was similar between patients with a progressive and a relapsing course. The average time to induce a response with prednisone (60 mg/day) was approximately 2 months, with maximal improvement not observed until after 6 months. One study showed improvement in disability scores within 2 weeks of starting 60 mg of daily prednisolone. A minority of patients have remained in remission after tapering steroids, but most (up to 70%) have relapsed after discontinuing treatment and have required repeated courses of prednisone or alternative immunotherapy.

In some patients the addition of azathioprine, cyclosporine A, mycophenolate mofetil, methotrexate, or other so-called “steroid-sparing” agents may sustain a remission and reduce or eliminate the requirement for high dose prednisone, but this benefit has not been confirmed in randomized controlled trials. Young age at onset, duration of symptoms less than 6 months, slight neurologic impairment, and mild slowing of nerve conduction velocities have been associated with a favorable response to corticosteroids. Rapid tapering of prednisone may increase the risk of relapse.

Most patients observe improvement in strength and sensory symptoms after several weeks of treatment. Maximal improvement occurs after 3 to 6 months of therapy, and only a minority of patients experience further recovery after 6 months. The standard dosage of prednisone is 1-1.5 mg/kg/day, administered as a single morning dosage. Weekly high-dose pulse intravenous or oral methylprednisolone or pulse weekly oral dexamethasone may be an effective alternative regimen with fewer side effects, but this has yet to be confirmed in large controlled trials.

Those who experience substantial clinical improvement after taking prednisone daily may reduce the dosage by switching to an alternate day regimen after 2 or 3 months and tapering by 5-10 mg on the alternate day, every 2 to 4 weeks, as gauged by the patient’s clinical state. If the patient deteriorates, the dosage should be increased to the minimum that induces improvement. Anecdotal reports suggest that adding an alternative treatment (PE, IVIg, Table 6

<table>
<thead>
<tr>
<th>Therapy for CIDP</th>
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<tbody>
<tr>
<td><strong>Proven Therapies from randomized controlled trials (Class I evidence):</strong></td>
</tr>
<tr>
<td>IVIg</td>
</tr>
<tr>
<td>Prednisone</td>
</tr>
<tr>
<td>Plasma exchange</td>
</tr>
<tr>
<td><strong>Therapies probably ineffective based upon randomized controlled trials (Class I evidence): These studies all had difficulties in trial design:</strong></td>
</tr>
<tr>
<td>Azathioprine</td>
</tr>
<tr>
<td>Interferon B1a</td>
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<tr>
<td>Methotrexate</td>
</tr>
<tr>
<td><strong>Therapies of unproven benefit but probably helpful as steroid sparing agents, based upon clinical experience, and &gt; 1 case series (Class IV evidence):</strong></td>
</tr>
<tr>
<td>Cyclosporine A</td>
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<tr>
<td>Cyclophosphamide</td>
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<tr>
<td>Azathioprine</td>
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<tr>
<td><strong>Other therapies of unproven benefit (Class IV evidence):</strong></td>
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<tr>
<td>Mycophenolate mofetil</td>
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<tr>
<td>Pulse weekly oral prednisolone</td>
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<tr>
<td>Pulse weekly oral dexamethasone</td>
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<tr>
<td>Pulse weekly intravenous methylprednisolone</td>
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<td>Rituximab</td>
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<tr>
<td>Interferon alpha 2a</td>
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<td>Etanercept</td>
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<td>Alemtuzumab</td>
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<td>Hematopoietic stem cell transplantation</td>
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CIDP = chronic inflammatory demyelinating polyneuropathy; IVIg = intravenous immunoglobulin.
azathioprine, cyclophosphamide, or cyclosporine A) should be considered in patients who develop adverse effects, relapse repeatedly following reduction of prednisone dosage, or require more than 35 mg of prednisone every other day.

Prednisone is best suited for younger patients with CIDP who have few other medical illnesses. Long-term prednisone therapy is generally poorly tolerated in the elderly and those who have concurrent medical conditions (e.g., hypertension, diabetes mellitus, obesity, peptic ulcer disease, osteoporosis). Weight, blood pressure, blood glucose, electrolytes, ophthalmological evaluation, and stool guaiac require regular monitoring. In addition, periodic bone density measurements and a regimen to prevent steroid induced osteoporosis should be instituted.

**Plasma Exchange**

Two short-term randomized, placebo-controlled trials have demonstrated that PE is superior to placebo, with response rates ranging from 33-80%. Improvement was observed in the mean Neurologic Disability Score, grip strength, and clinical disability grade. Summated mean motor potential amplitudes and CVs also increased after treatment. Patients improved within 4 weeks after initiating therapy, and those with a chronic progressive course responded as well as patients with relapsing disease. Although the short-term efficacy of PE has been convincingly demonstrated, 50-67% of patients have deteriorated weeks to months after treatment and have required repeated exchanges or an alternative therapy to maintain improvement.

Long-term outpatient PE can be used successfully in selected patients with peripheral access maintained with an arteriovenous fistula (Richard Barohn, MD, personal communication). Alternatively, combining prednisone or other immunosuppressive agents with PE may induce a prolonged remission. Those with a short duration of disease, and EMG or pathological features of a primary demyelinating neuropathy (without axonal loss) are more likely to respond to PE. Dyck and colleagues have established that the short-term efficacy of PE is similar to IVIg.

The beneficial effect of PE presumably results from the removal of pathogenic humoral factors, such as circulating immunoglobulins or auto-antibodies. A single exchange removes 3 to 5 liters of plasma and reduces intravascular IgG by approximately 45%, so that 3 to 5 exchanges are required to remove approximately 90% of IgG. The exchanged plasma is replaced with 5% albumin and saline, sometimes supplemented with calcium, and acid-citrate dextrose or heparin.

Although no specific guidelines have been established for the frequency or schedule of treatment, the frequency of PE can be guided by the duration of a clinical response. For example, those with severe disability (e.g., nonambulatory) are generally treated with 5 exchanges (each exchange 250 cc/kg) performed over a period of 7 to 10 days. Improvement usually occurs within several weeks followed by a stable phase of weeks to months. Exchanges may be repeated periodically in a similar fashion as necessary to maintain improvement. Those who have mild or moderate disability and remain ambulatory may benefit from 2 or 3 exchanges per week over a period of 2 to 3 weeks, followed by once or twice weekly exchanges for an additional 3 weeks.

**Intravenous Immunoglobulin**

IVIg has been introduced as the main therapy for CIDP over the last decade. Although early studies showed variable results, five well-controlled studies have demonstrated that approximately 50-70% of patients respond to IVIg. Improvement occurs within a few weeks; rarely, recovery may be dramatic, within 1 or 2 days after completing the infusion. Usually the benefit is transient (1 to 6 weeks) with 50% of patients relapsing within weeks to months, and subsequently requiring regular infusions to maintain maximum improvement. Patients with a progressive course or predominantly sensory deficits with tremor may be less likely to improve. Mendell and colleagues showed that 11 of 29 treatment naïve patients with CIDP improved 1 or more disability grades after receiving 1 g/kg/day of IVIg at baseline and after 3 weeks compared to 2 of 21 patients who received placebo; 76% of IVIg treated patients had improved strength. Improvement was noted as early as 10 days after therapy.

The recently published Immune Globulin Intravenous CIDP Efficacy trial (ICE trial) was the largest and longest randomized, double-blind placebo-controlled study demonstrating sustained efficacy of 1 gm/kg of IVIg administered every 3 weeks for 6 months in patients with CIDP. Outcomes showed that 54% of treated patients responded with substantial improvement in measures of strength, functional disability, and quality of life compared to placebo-treated patients. These outcomes, in conjunction with prior IVIg treatment trials, have established that IVIg is the standard of care and should be the initial treatment of choice for patients with CIDP. IVIg has been granted a Food and Drug Administration indication for this condition.

As with PE, anecdotal reports suggest that combining IVIg with prednisone or other immunosuppressive medications may further augment the duration of remission and reduce the frequency of IVIg infusions. Most future clinical trials in CIDP will incorporate IVIg therapy as standard of care treatment in the trial design.

The standard dosage is 2 gm/kg administered intravenously over 2 to 5 days. For patients who relapse and require periodic treatment at intervals from 1 to 4 weeks to maintain improvement, the addition of an oral immunosuppressant can be offered to decrease the frequency of IVIg administration. The ICE trial demonstrated that clinical stability can be achieved with 1 gm/kg of IVIg administered every 3 weeks. Once the patient has stabilized, most tolerate dosage reduction or increase of the treatment interval and still maintain clinical stability. In a few cases, subcutaneous IVIg has also been administered successfully as maintenance therapy.

IVIg is contraindicated in patients with absolute IgA deficiency or a history of a previous allergic reaction following exposure to human immune globulin. Minor side effects are common and include
headache, malaise, fatigue, and fever. Other adverse effects include: aseptic meningitis; rashes; myalgias; flushing; fluid overload with edema or congestive heart failure; renal insufficiency (presumably due to hyperosmolarity); transient neutropenia; back, chest, leg, or abdominal pain; and eczematous rash. Rarely, IVIg induces a hyperviscosity syndrome with increased risk for deep venous thrombosis, myocardial ischemia, or stroke.

**ALTERNATIVE IMMUNOSUPPRESSIVE REGIMENS**

The indications for considering alternative immunosuppressive agents for patients with CIDP are: (1) no improvement with sequential or combined trials of conventional therapies that have demonstrated efficacy in randomized controlled trials; (2) improvement with these treatments, but with frequent relapses that make continued therapy cumbersome, time-consuming, and costly; or (3) intolerable adverse effects with the proven therapies. Single case reports, open label case series, and retrospective reviews have shown that most of the agents reviewed in this section are effective in some patients with CIDP. Few of them, however, have been submitted to rigorous clinical trials that establish efficacy. In other cases, some of the agents (e.g., azathioprine, methotrexate, interferon B1a) have been carefully studied in larger controlled trials and proven ineffective.

There are several explanations why these drug trials were negative, including lack of appropriate duration of treatment (e.g., for azathioprine, the endpoint of the trial was 9 months, but it was subsequently recognized that benefit may not be observed for 12-18 months); complex trial design (e.g., in the methotrexate trial, patients were on varying tapering doses of IVIg or prednisone); lack of adequate power to detect a significant response due to small sample size (azathioprine, interferon B1a); and a surprisingly high placebo response in patients assigned to the placebo arm of several studies (up to 40% in the methotrexate and interferon B1a trials), suggesting that many patients did not relapse as anticipated when IVIg was discontinued.

The last, and perhaps most important conclusion, is that these agents simply may not be effective treatments for CIDP. Accordingly, it is prudent to advise patients that they are unlikely to be more effective than proven therapies, and to maintain realistic expectations about recovery. This is particularly true in those with a prolonged disease course and concomitant severe axon loss, in whom the neurological deficit may be irreversible. For those individuals, a reasonable expectation would be to stabilize the condition and halt further progression.

**Azathioprine**

Although anecdotal reports have indicated that azathioprine is an effective therapy for CIDP, one randomized study of only 9 months duration showed that the degree of improvement with azathioprine combined with prednisone was similar to prednisone alone. However, the immunosuppressive effects of this agent may not occur for over one year, as previously noted, and therefore, the duration of this trial was too short to exclude benefit. Others have found that azathioprine is helpful in some patients not only for stabilizing the disease course, but more importantly, for allowing reduction of prednisone dosage. Therefore, azathioprine is ideally used as a steroid-sparing adjunctive agent for CIDP treatment.

The usual dosage is 2-3 mg/kg/day administered orally as a single daily dose. A test dose of 50 mg/day may be given for the first week. If this is tolerated, the dose can be gradually increased by 50 mg every few days. A complete blood count and liver enzymes should be monitored monthly for 6 months, and then every 3 months thereafter. An acute hypersensitivity reaction may occur in the first several days to weeks of therapy, characterized by severe nausea and vomiting, diarrhea, fever, malaise and myalgias, rash, elevation in liver enzymes, and pancreatitis. These adverse effects are reversible upon discontinuation of the drug.

**Cyclosporine A**

Patients with refractory CIDP may improve with cyclosporine A. Although published experience with this drug is restricted to several small case series, response rates have ranged from 40-90%. Patients improved within weeks of initiating treatment, and several discontinued prednisone without clinical deterioration. The initial dosage is 5 mg/kg/day orally, in 2 divided dosages, and adjustments are made by following target blood levels. Once the patient has stabilized, the dosage should be titrated to the lowest dose required to maintain improvement.

Cyclosporine A is contraindicated in patients with systemic infection, history of previous hypersensitivity reaction, abnormal renal function, uncontrolled hypertension, and malignancy. Blood pressure, renal function (including creatinine clearance), serum lipids, magnesium, and potassium levels require regular monitoring. Checking trough serum cyclosporine levels may minimize toxicity. The recommendation is for a trough level between 100 and 200 ng/mL. The main side effects of cyclosporine A are renal insufficiency, hypertension, hirsutism, tremor, gingival hyperplasia, increased risk of opportunistic infection, sepsis, nausea, vomiting, hepatotoxicity, headache, and cramps.

**Mycophenolate Mofetil**

Mycophenolate mofetil (MMF) is a novel immunosuppressant that has been used successfully for prevention of organ rejection after renal transplantation, and may be appropriate for the treatment of immune-mediated neuromuscular diseases. MMF inhibits the de novo pathway of purine nucleotide synthesis, thereby blocking the proliferation of B and T-cell lymphocytes. MMF produces immunosuppression that is comparable to azathioprine without causing major bone marrow suppression. Several open-label, unblinded case series have reported improved strength, clinical stability, and successful tapering of prednisone or IVIg in patients with CIDP. Larger, randomized, controlled trials may further clarify the role of this agent in CIDP. The drug is appealing because it is easy to use, well-tolerated, and has few long-term adverse effects.
Cyclophosphamide

Oral cyclophosphamide has also proven beneficial for patients with CIDP when administered for several months as monotherapy or in combination with prednisone. Uncontrolled case series suggest monthly, pulse intravenous cyclophosphamide is effective when combined with prednisone or administered after cycles of PE. Good and colleagues reported that 12 of 15 CIDP patients who were refractory to PE, IVIg, or steroids improved with monthly intravenous pulse cyclophosphamide (1 g/m\(^2\)); the average time to sustained improvement was 8.5 months.\(^6\) Complications included nausea, headache, rash, and an anticipated leukopenia. No patient developed severe bone marrow suppression or malignancy with an average follow-up of 3 years.

Other reports have highlighted a treatment response following high-dose cyclophosphamide and myeloablative chemotherapy with autologous stem cell rescue. Because of the potential for serious adverse effects, particularly immunosuppression and risk for opportunistic infection and sepsis, cyclophosphamide has traditionally been reserved for patients with CIDP who fail conventional immunotherapy and has been administered in conjunction with prednisone, IVIg, or PE.

With increasing experience, this agent has been used effectively as monotherapy and may be especially effective in those with severe disability or frequent relapses despite conventional therapy. It is exceptionally well-tolerated when administered as monthly intravenous pulse therapy; many patients have preferred this approach to long-term daily prednisone. The response rate has been reported to be as high as 80% in retrospective case series.

Leukopenia is a common adverse effect and a complete blood count with differential, platelet count, and urinalysis should be checked 2 weeks after intravenous administration. The dosage should be adjusted by 25% increments to produce a transient reduction of the white blood cell count to 1-2 K/\(\mu\)L. Significant nausea can be avoided by administering ondansetron hydrochloride (8 mg by mouth, twice daily) or other antiemetics, and at least 3 liters of intravenous fluid should be given prior to and during the infusion to reduce the risk of hemorrhagic cystitis.

The standard intravenous dosage is 1 gm/m\(^2\) administered monthly for 6 to 12 months. Other protocols include oral daily cyclophosphamide at dose of 1-2 mg/kg/day or high dose myeloablative therapy at 200 mg/kg over 4 days. The latter regimen is highly toxic and should only be considered by experts in CIDP who have experience with this protocol. The main side effects of cyclophosphamide are dose-dependent bone marrow suppression, consequent reduced resistance to infection, hemorrhagic cystitis, infertility, teratogenic effects, amenorrhea, nausea, vomiting, anorexia, alopecia, and malaise. A history of previous bone marrow suppression or myelodysplastic syndrome is a contraindication to treatment with cyclophosphamide.

Interferons

Interferons have complex immunomodulating effects and may influence the levels of proinflammatory cytokines, especially tumor necrosis factor alpha, interleukin-2, and interferon gamma, which have a role in the development of inflammatory demyelination. Several case reports and one prospective, unblinded pilot study indicated that interferon alpha 2a was effective in patients with CIDP who were refractory to conventional immunomodulating agents. No randomized controlled trials with this agent have been conducted, and significant adverse effects, including fever, malaise, and flu-like symptoms following each injection often preclude its long-term use in some patients.

Similarly, initial reports indicated that interferon B1a was effective in several patients with CIDP who did not improve after trials of prednisone, PE, cyclosporine A, IVIg, and azathioprine. A prospective, multicenter, open-label trial of interferon B1a (30 ug intramuscular weekly) for 6 months in 20 patients with CIDP showed significant improvement in the neurological disability score and clinical grading scale compared to baseline measures. However, a prospective, randomized, double-blind, placebo controlled trial of interferon B1a (30 or 60 ug twice weekly for 4 months) in 67 IVIg-dependent CIDP patients did not show clinical improvement or reduced IVIg dosing in treated patients compared to placebo.

Post-hoc analysis indicated that a subset of more severely affected patients who required higher doses of IVIg at baseline did improve. Furthermore, the conclusions regarding lack of efficacy of interferon B1a cannot be considered definitive as the study was underpowered due to poor patient recruitment, and there was a surprisingly high rate (40%) of placebo responders.

Methotrexate

Methotrexate has been a safe and effective agent for patients with inflammatory myopathies and other connective tissue disorders and has been used as a steroid sparing drug for decades. Several open-label case reports and series have suggested a beneficial role in CIDP. However, a randomized, double-blind, placebo-controlled trial of escalating doses of methotrexate in steroid or IVIg treated CIDP patients showed no benefit over placebo. The trial design was complicated, the placebo response was high, and the maximum dose of methotrexate (15 mg/week) was low. Therefore, the role of this agent as a steroid or IVIg sparing agent in patients with CIDP remains uncertain.

Other Immunosuppressants

Case reports or small series have indicated potential efficacy of rituximab, etanercept, alemtuzumab, and hematopoietic stem cell transplantation in treatment refractory CIDP. Until more data are available, these treatments should be considered experimental.
SUPPORTIVE THERAPIES

Patients certainly benefit from walking sticks, walkers, ankle-foot orthotics, and other rehabilitation devices and strategies to assist ambulation and other activities of daily living. Physical and occupational therapy may help maintain range of motion, prevent joint contractures in paretic limbs, and assist in gait retraining. A moderate exercise regimen may help reduce physical fatigue and increase endurance.

CONCLUSION

Initial descriptions of this disease highlighted the substantial disability that accrued in most patients. With earlier recognition of the disorder by neurologists and more effective and aggressive management strategies, the overall prognosis is probably more favorable. With treatment, more than two-thirds of patients remain independent and able to work. Others have reported that as many as 90% improve with therapy, but 50% relapse within a few years and fewer than 33% remain in remission without therapy.

Recent experience suggests that approximately 10-15% of patients have a complete remission with a normal neurological examination and no functional disability. Conversely, several large series have suggested that approximately 5-10% of patients die from their illness or the complications of treatment. Greater disability and a poorer long-term prognosis have been correlated with an older age of onset (> 30 years), four limb weakness at onset, progressive course, central nervous system involvement, and prominent axonal loss on nerve biopsy. Clinical experience suggests that the two most clinically important negative prognostic factors are severe axon loss with prominent atrophy on examination and long duration of the disease course.

REFERENCES

An area of peripheral neuropathy (PN) that poses great concern to patient and clinician alike is paraprotein-associated neuropathy. Notably, peripheral disorders associated with monoclonal gammopathies are usually discovered in about 10% of patients presenting with complaints diagnosed as PN. This discovery warrants further evaluation for underlying plasma cell dyscrasias, some of which signify life threatening disease, but most of which are benign. The most frequent monoclonal disorders associated with neuropathy are smoldering myeloma, multiple myeloma (MM), Waldenström macroglobulinemia (WM), solitary plasmacytoma, systemic immunoglobulin light chain amyloidosis (AL), polynuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS), and cryoglobulinemia. If these ominous conditions are excluded by careful evaluation, the patient is classified as having monoclonal gammopathy of undetermined significance. Diagnostic criteria for these disorders, risk factors to determine prognosis, and current management principles will be further discussed.

ParaproteinemiaAssociated Neuropathy

Plasma cell dyscrasias, known as paraproteinemias or monoclonal gammopathies, are further classified by the proliferation of individual clones of β lymphocytes that secrete excess monoclonal antibodies. This excess production of plasma cells can be either neoplastic or a low grade, potentially neoplastic process. Monoclonal proteins can be found in approximately 3% of the population 50 years or older with rates increasing with age. Prevalence rates are higher for men than women and African Americans have a three-fold higher age-adjusted prevalence rate than those who are Caucasian. These paraproteinemias are usually asymptomatic and are found on routine blood testing without associated abnormalities. Nevertheless, certain disease associations occur more often than by chance and include: (1) monoclonal gammopathies of undetermined significance (MGUS), biclonal gammopathies, idiopathic Bence Jones proteinuria; (2) the malignant monoclonal gammopathies of MM, smoldering multiple myeloma (SMM), WM, uncommon malignant disorders of solitary plasmacytoma and POEMS syndrome; (3) systemic immunoglobulin AL amyloidosis; (4) cryoglobulinemia; and (5) heavy chain diseases. When clinical features are present, they can vary from fatigue, weight loss purpura, congestive heart failure, nephrotic syndrome, PN and orthostatic hypotension, to mucocutaneous bleeding.

Paraprotein associated neuropathies have become recognized as an important category of late onset chronic polyneuropathies, warranting further evaluation for an underlying plasma cell dyscrasia. In patients presenting with PN of unknown cause, 10% will have a monoclonal protein, the majority of whom will be found to have MGUS. This is of even greater importance in patients with patterns of nerve conduction abnormality suggestive of demyelination, autonomic dysfunction, predominantly motor neuropathy, or lower motor neuron (MN) findings. The plasma cells disorders most often associated with neuropathy include MGUS, SMM, MM, WM, solitary plasmacytoma, systemic AL amyloidosis, and POEMS.

It is helpful to distinguish between a monoclonal or a polyclonal process in plasma cell disorders because unlike the monoclonal process, a reactive or inflammatory process commonly causes the polyclonal increase in immunoglobulin (Ig). Polyclonal Igs are produced by many clones of plasma cells. Blood levels of polyclonal
gamma globulin of 3g/dL or more are associated with liver disease, connective tissue diseases, chronic infections, and nonhematologic malignancies.7

On the other hand, and in particular for the physician caring for patients with neuropathy, the monoclonal process is more often associated with premalignant or malignant disease than its polyclonal counterpart. There can be an overlap in antibody mediated pathogenic mechanisms among these different monoclonal and polyclonal antibodies.8

Monoclonal proteins (also called M proteins, myeloma proteins, or paraproteins) consist of two heavy polypeptide chains of the same class and subclass, and two light polypeptide chains of the same type. The different monoclonal proteins are known by letters that correspond to the class of their heavy chains, which are designated by Greek alphabet characters: γ (gamma) in IgG, α (alpha) in IgA, μ (mu) in IgM, δ (delta) in IgD, and ε (epsilon) in IgE. There are four subclasses for IgG, two subclasses for IgA, and no subclasses for IgM, IgD, or IgE. The light chain types are kappa (κ) and lambda (λ). Each of these monoclonal proteins is produced by a proliferation of single clonal population of plasma cells in the bone marrow. The mechanism of monoclonal expansion of a single Ig secreting plasma cell population is unknown in most instances.4 However, a review of the data by Kyle and Rajkumar9 suggests that in at least 50% of MGUS cases, there is evidence of genomic instability on molecular genetic testing that includes primary chromosomal translocations at the Ig heavy chain locus 14q32 (50%), hyperdiploidy (40%), or unknown (10%).8,10-12 The cause for this genomic instability is uncertain. However, current evidence suggests that antigenic stimulation related to infection and immune dysregulation may be an important factor.9 Additional contributors to the progression of MGUS to multiple myeloma are under study and include changes in the micro environment via induction of angiogenesis, suppression of cell-mediated immunity, adhesions of myeloma cells to stroma, alteration of adhesion molecules, and stromal cytokine over expression.9

Increased osteoclast activation and receptor activator of nuclear factor kappa beta B ligand and decreased levels of osteoprotegerin result in lytic bone lesions and osteoporosis.7,9,12 The pathogenic link between the monoclonal proteins and nerve damage is known only in a few instances. In the IgM class, it is thought that neuropathy is related to the reactivity of the circulating antibodies that are directed against specific neural antigens expressed on the peripheral nerves such as myelin-associated glycoprotein (MAG), chondroitin sulfate, and sulfatide with consequential complement dependent nerve damage.8 Although it remains unproven, findings have shown the deposition of IgM protein within the myelin in both large and small myelinated fibers may have a role in the pathogenesis of neuropathy.5,13,14

**Discovery of Monoclonal Proteins**

The best methods of identifying M proteins are serum protein electrophoresis techniques. The immunofixation process distinguishes the Ig class and type of light chain. Densitometry is used to measure the monoclonal protein that is visible on serum electrophoresis and has replaced the use of nephelometry as a more reliable way to measure Ig levels. A 24 hour analysis of urine for protein excretion and a urine protein electrophoresis and immunofixation is warranted to detect and quantify the monoclonal protein in the urine. To date, this has been the standard recommendation.15 A recent study by Katzmann and colleagues suggests this may not be necessary due to the highly sensitive serum free light chain assay now available.16 Measurement of β2-microglobulin has not proved predictive of malignant transformation and is no longer recommended. If a monoclonal protein is found, additional hematological studies, (serum calcium, complete blood count, and serum creatinine) are needed. While a skeletal survey and aspirated bone marrow biopsy are generally performed to rule out myeloma, they are not considered necessary when other laboratory tests are normal and the serum monoclonal spike is less than 1.5 g per dL and other laboratory test are normal.15 If abnormalities are detected on these tests, appropriate tissue biopsy is recommended to exclude amyloidosis. When no monoclonal protein is uncovered, patients with motor polyradiculoneuropathy with demyelinating features on nerve conduction studies (NCSs) should have cerebrospinal fluid examination (CSF) , skeletal bone survey, and sural nerve biopsy (Figure 1). Sural nerve biopsy has shown mixed pathology (fiber loss, segmental demyelination, and axonal degeneration). In the IgM class, a predominantly demyelinating process is often observed. Patients with progressive axonal neuropathies with autonomic dysfunction require biopsy of one or more appropriate tissues to rule out or confirm amyloidosis.17

**Electrodiagnostic Studies**

Plasma cell disorders demonstrate abnormalities consistent with both peripheral demyelination and axonal degeneration (Table 1). NCSs are typically abnormal in motor and sensory fibers in the both the upper extremities (UEs) and lower extremities. Motor nerve conduction velocities (MNCV) are often decreased below the lower limits of normal by 20% or more. Sensory nerve action potentials (SNAPs) are consistently reduced in amplitude or are unobtainable, with more pronounced changes in the lower limb nerves. Frequently F-wave latencies are prolonged, but not out of proportion to the degree of peripheral nerve conduction slowing. In IgM neuropathies, the nerve conduction abnormalities tend to be more severe than in cases involving other protein classes. Needle electromyography (EMG) examination demonstrates changes consistent with active denervation (increased insertional activity with fibrillation potentials) in over 80% of patients. Evidence of concomitant demyelination and axonopathy is very common. The sural sensory nerve more often shows damage than the median sensory nerve.4

**Monoclonal Gammopathy of Undetermined Significance**

Typically presenting asymptomatically after the fifth decade of life, MGUS is the most common plasma cell dyscrasia found in
It is considered a premalignant disorder characterized by low grade monoclonal plasma cell proliferation in the bone marrow and the absence of end-organ damage. In de novo paraproteinemia, about two-thirds of the time after exclusion of amyloidosis, MM, or osteosclerotic myeloma, WM, lymphoma or lymphoproliferative disease, no identifiable cause is found and the disorder by exclusion is classified as MGUS. While characterized as premalignant, it is not strictly “benign” in that it is epidemiologically linked to a lifelong risk of progression to multiple myeloma or related disorders, requiring lifelong follow up necessary in all persons.19

In addition to those with MGUS, an M protein is found in 3 to 4% of patients with a diffuse lymphoproliferative process, in the sera of patients with chronic lymphocytic leukemia with no recognizable effect on the clinical course, in the dermatological diseases of lichen myxedematous, pyoderma gangrenosum, and necrobiotic xanthogranuloma and more often in the peripheral neurological disorders sensorimotor PN and chronic inflammatory demyelinating polyneuropathy (CIDP). MGUS occurs in approximately 5 to 10% of adult patients with chronic idiopathic axonal polyneuropathy, which represents a six-fold increase over the rate found in the general population.20

The most common clinical presentations of MGUS polyneuropathy are often similar among the different classes of protein and usually begin in the sixth decade, progressing in a slow insidious pattern as distal symmetrical sensorimotor polyneuropathy. Sensory deficits begin in the toes and extend up the lower limbs to a greater extent then the UEs. Muscle stretch reflexes are globally diminished or absent with almost universal sparing of cranial nerve function. Paresthesia, ataxia, and pain may be significant, but seldom lead to complete inability to walk. The neuropathy in MGUS tends to be more relentlessly progressive than the typical relapsing remitting course of CIDP. Differentiating a patient with MGUS from one with another plasma cell disorder is difficult on clinical grounds alone. Use of laboratory and additional diagnostic study findings are often helpful in this regard. The recommended diagnostic criteria in patients with suspected MGUS are summarized in Table 2. The initial studies to include are a complete blood count, serum creatinine, and serum calcium. If irregularities are identified in any of these tests, a plain film x-ray bone survey including long bones (the humerus and femur bilaterally) is performed. A bone marrow aspirate and biopsy are recommended if the M-protein value is > 1.5g/dL, an IgA or an IgM MGUS is identified, or a patient with an abnormal serum free light chain (FLC) ratio is encountered.21

Electrophysiological studies in paraproteinemimic neuropathy often show findings suggesting demyelination or both demyelination and axonal degeneration. In such cases, MNCVs are reduced below the lower limits of normal and SNAPs are consistently reduced...
and their response to treatment. IgM MGUS is distinguished from IgG and IgA by several features: it is over represented in the neuropathy group when compared with the other classes, sensory ataxia occurs more frequently, NCSs are more often demyelinating, are significantly worse, and are more frequently accompanied by dispersion of motor responses. Additionally, within the IgM MGUS group, there is interest in the role that frequently associated antibodies (anti MAG antibody occurs in about 50% of the patients with IgM MGUS) may play in these neuropathies. If these antibodies prove to be pathogenic, treatments directed at antibody reduction may be efficacious. Additional monoclonal IgM antibodies react to other peripheral nerve antigens, including chondroitin sulfate C, sulfatide, cytoskeletal proteins, trisulfated

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<th>Disorder</th>
<th>Disease definition</th>
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<td>MGUS</td>
<td>Serum monoclonal protein level &lt; 3 g/dL, bone marrow plasma cells &lt; 10% and absence of end-organ damage, such as lytic bone lesions, anemia, hypercalcemia or renal failure that can be attributed to a plasma cell proliferative disorder.</td>
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<td>SMM</td>
<td>Serum monoclonal protein (IgG or IgA) level &gt; 3g/dL and/or bone marrow plasma cells &gt; 10%, absence of end such as lytic bone lesions, anemia, hypercalcemia or renal failure that can be attributed to a plasma cell proliferative disorder.</td>
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<td>Multiple Myeloma</td>
<td>Bone marrow plasma cells &gt; 10%, presence of serum and/or urinary monoclonal protein (except in patients with true nonsecretory multiple myeloma), plus evidence of lytic bone lesions, anemia, hypercalcemia or renal failure that can e attributed to a plasma cell proliferative disorder.</td>
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<td>Waldenström macroglobulinemia</td>
<td>IgM monoclonal gammopathy (regardless of the size of the M protein) with &gt; 10% bone marrow lymphoplasmacytic infiltration (usually intertrabecular) by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation a typical immunophenotype (eg. surface IgM+, CD5+, CD10-, CD19+, CD20+, CD23-, that satisfactorily excludes other lymphoproliferative disorder, including chronic leukemia and mantle cell lymphoma. Note: IgM MGUS is defined as serum IgM monoclonal protein level &lt; 3g/dL, bone marrow lymphoplasmacytic infiltration &lt; 10% and no evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy or hepatosplenomegaly. Smoldering Waldenström macroglobulinemia (also referred to as indolent or asymptomatic Waldenström macroglobulinemia) is defined as serum IgM monoclonal protein level &gt;3 g/dL and/or bone marrow lymphoplasmacytic infiltration &gt; 10% and no evidence of end-organ damage, such as anemia, constitutional symptoms, hyperviscosity, lymphadenopathy or hepatosplenomegaly that can be attributed to a plasma cell proliferative disorder.</td>
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<td>Solitary plasmacytoma</td>
<td>Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells, normal bone marrow with no evidence of clonal plasma cells, normal skeletal survey and MRI of spine and pelvis, a absence of end-organ damage, such as lytic bone lesions, anemia, hypercalcemia or renal failure that can be attributed to a plasma cell proliferative disorder.</td>
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<td>Systemic AL amyloidosis</td>
<td>Presence of an amyloid-related systemic syndrome (such as renal, liver, heart, gastrointestinal tract, peripheral nerve, or muscle involvement) with positive amyloid staining by Congo red in any tissue (eg fat, aspiration bone marrow or tissue biopsy), plus evidence that amyloid is light chain related established by direct examination of the amyloid (immunoperoxidase staining, direct sequencing, etc), plus evidence of a monoclonal plasma cell proliferative disorder (serum and urine M protein, abnormal free light chain ratio, or clonal plasma cells in the bone marrow) Note: Approximately 2-3% of patients with AL amyloidosis will not meet the requirement for evidence of a monoclonal plasma cell disorder; the diagnosis of AL amyloidosis must be made with caution in these patients.</td>
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<td>POEMS syndrome</td>
<td>Presence of a monoclonal plasma cell disorder, peripheral neuropathy and at least 1 of the following 7 features: osteosclerotic myeloma, Castleman disease, organomegaly, endocrinopathy (excluding diabetes mellitus or hypothyroidism) edema, typical skin changes and papilledema. Note Not every patient who meets these criteria will have POEMS syndrome; the features should have a temporal relationship to each other and no other attributable cause. The absence of either osteosclerotic myeloma or Castleman disease should make the diagnosis suspect. Elevation in plasma or serum levels of vascular endothelial growth factor and thrombocytosis are common features of the syndrome and are helpful when the diagnosis is difficult.</td>
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</tbody>
</table>

AL = light chain; Ig = immunoglobulin; MGUS = monoclonal gammopathy of undetermined significance; MRI = magnetic resonance imaging; SMM = smoldering multiple myeloma; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathies, and skin changes; Used with permission from Rajkumar SV, Dispenzieri A, & Kyle RA. (2006).
A decision to treat is dependent on the severity and temporal path of the neuropathy. A patient may mandate watchful waiting. However, if the neuropathy is severe and meets diagnostic criteria for CIDP, the patient may respond to plasma exchange, but those with IgM MGUS have responded to plasma exchange, but those with IgM MGUS have not.21

Table 2 Risk Stratification Model to Predict progression of Monoclonal Gammopathy of Undetermined Significance to Myeloma or Related Disorders*

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>No. of patients</th>
<th>Relative Risk</th>
<th>Absolute risk of progression at 20 y (%)</th>
<th>Absolute risk of progression at 20 y accounting for death as a competing risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (serum M protein level &lt; 1.5 g/dL, IgG subtype, normal free light chain ratio [0.26-1.65])</td>
<td>449</td>
<td>1.0</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Low to intermediate risk (any 1 factor abnormal)</td>
<td>420</td>
<td>5.4</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>High to intermediate risk (any 2 factors abnormal)</td>
<td>226</td>
<td>10.1</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>High Risk (all 3 factors abnormal)</td>
<td>53</td>
<td>20.8</td>
<td>58</td>
<td>27</td>
</tr>
</tbody>
</table>


Even though MGUS is a common finding in clinical practice, determining whether it will remain stable or progress to multiple myeloma is a significant challenge. The rate of malignant progression is about 1% per year. When other causes of death are factored in, it is approximately 11% at 25 years of age. A risk stratification system (see Table 3) can predict the risk to progression of MGUS based on three factors: size of the M protein value being the most important predictor (the risk of progression of a serum M-protein of 1.5 g/L being twice the risk of progression with a value of 5 g/L); the type of Ig and the serum FLC ratio.6,18,22 Patients with MGUS need indefinite monitoring with repeat short latency somatosensory evoked potentials every 6 to 12 months. Although the natural history of evolution of MGUS to malignancy is unknown, genetic changes, bone marrow angiogenesis, and various cytokines related to myeloma bone disease and possibly infectious agents may all play a part. The treatment for MGUS neuropathy is unclear. A decision to treat is dependent on the severity and temporal path of the neuropathy. An indolent course and minor deficits may mandate watchful waiting. However, if the neuropathy is severe and meets diagnostic criteria for CIDP, the patient may respond to immunomodulatory therapies. The response rates to plasmapheresis, intravenous immunoglobulin (IVIg), prednisone or combinations have been promising. A double blind placebo controlled trial of intermittent cyclophosphamide with prednisone over a 6 month study period in IgM MGUS neuropathy failed to show beneficial effects on functional scales but did appear to measurably enhance muscle strength and sensation.41 A more recent randomized placebo controlled clinical trial of rituximab in IgM anti myelin associated glycoprotein demyelinating neuropathy with small patient numbers demonstrated a significant improvement in time of a 10 m walk in the rituximab group.42 Despite treatment, when there is a rapid clinical deterioration of the neuropathy, reevaluation for underlying malignant lymphoproliferative disorders or amyloidosis is prudent.5

Multiple Myeloma and Smoldering Multiple Myeloma

SMM accounts for 15% of all cases of newly diagnosed multiple myeloma. Similarly to MGUS, SMM is classified as an asymptomatic premalignant condition. MGUS and SMM are distinguished from each other based on the size of the serum M protein and bone marrow plasma cell percentage. Unlike MGUS, the risk to progression to MM is much higher in SMM: 1% in MGUS versus 10 to 20% in SMM. Most patients with SMM progress to MM in 3 to 4 years with some variability.23 Like MGUS, treatment for SMM is based on observation alone, but with more frequent follow up: typically every 3 to 4 months.24

MM is distinguished by the propagation of a single clone of plasma cells engaged in the production of a specific Ig. MM evolves from a premalignant state of MGUS through unknown mechanisms. This neoplastic process occurs in the bone marrow and invades adjacent bone causing skeletal destruction.24 Bone pain (particularly in the back or chest), weakness, pallor, and fatigue are the typical presenting clinical features. Renal insufficiency, hypercalcemia, and anemia are other key clinical flags. Organ involvement includes the kidneys, less commonly, the liver, and there is an increased propensity for neurological involvement that is most often in the form of compression of adjacent neural structures. Neurological complications are usually related to compression of the spinal cord or roots from lytic vertebral lesions and symptoms are localized.25 PN associated with MM is rare and occurs in about 5% of patients, usually presenting as a distal sensorimotor polyneuropathy. NCSs and sural nerve biopsy are typically consistent with an axonal process with a loss of myelinated fibers.25
The incidence of MM is approximately 4 per 100,000 per year and accounts for 1% of all malignant disease. Diagnostic criteria for MM includes the presence of bone marrow plasma cells > 10%, presence of M-protein, and evidence of lytic bone lesions or other underlying organ failure that can be attributed to an underlying plasma cell disorder (Table 2). Because AL amyloidosis complicates MM in 30 to 40% of cases, it is recommended that patients with MM have tissue or nerve biopsy performed to identify amyloidosis. Treatment for MM consists of radiation therapy, chemotherapy, autologous peripheral stem cell transplantation with conventional therapy, and novel targeted research trials.

### OTHER FORMS OF MULTIPLE MYELOMA

#### Solitary Plasmacytoma

Solitary plasmacytoma (SP) may be confined to bone or arise in extramedullary sites. There are a few reports of an association between solitary myelomas and PN. The presence of biopsy proven solitary lesion of bone or tissue with evidence of clonal plasma cells and the absence of end organ damage is suggestive of plasmacytoma (see further diagnostic criteria in Table 2). A magnetic resonance scan of the spine and pelvis should be performed in addition to a skeletal survey because one third of SP patients may have additional
POEMS Syndrome

POEMS syndrome is a rare atypical plasma cell proliferative disorder which can present as single or multiple plasmacytomas with one or more osteosclerotic lesions. The syndrome is important to recognize among the plasma cell disorders because it is treatable. The more common acronym POEMS is used to describe major clinical manifestations of the syndrome. However, variable additional key features including Castleman disease (giant lymph node hyperplasia, angiofollicular lymph node hyperplasia), papilledema, peripheral edema, ascites, polycythemia, thrombocytosis, and fatigue and clubbing are not included in the acronym. POEMS syndrome has been referred to as osteosclerotic myeloma, Crow-Fukase syndrome, plasma cell dyscrasias, endocrinopathy, and polyneuropathy syndrome, and Takatsuki syndrome.

While POEMS syndrome occurs in about 2% of patients with MM, this neuropathy differs from that associated with MM in several aspects. It occurs at an earlier age (median age of 51 years), is more commonly seen in men. POEMS neuropathy is more frequently a demyelinating predominantly motor neuropathy with slowed MNCVs and elevated CSF protein levels. An M protein is found in 90% of cases, and is most often composed of λ light chains associated with IgG and IgA heavy chains. Approximately 85% of these patients present with a PN, bearing a striking resemblance to CIDP with symmetrical proximal, distal weakness, and variable sensory loss. The clinical and electrophysiological similarities between CIDP and POEMS reinforce the importance of M protein screening on all patients presenting with acquired demyelinating neuropathy.

Additional clinical features include sclerotic bone lesions (primarily in the axial skeleton), a varying spectrum of the aforementioned associated clinical abnormalities, and respiratory problems. The pathogenesis is unclear, but is believed to be due in part to cytokine mediated with elevated vascular endothelial growth factor levels. The clinical course may vary from indolent to fulminatory due to the increased risk of full blown MM.

About one third of the patients with WM will have symptoms of PN. The typical neurologic presentation is chronic symmetric, predominantly sensory polyneuropathy, similar to the neuropathy associated with MGUS. Pure sensory polyneuropathy, multiple mononeuropathies and painful predominantly sensory neuropathy with prominent dysautonomia often associated with disordered gait are other clinical presentations. The central nervous system is rarely affected. When IgM binds to MAG or sulfatide, there is an associated increase in the frequency and severity of peripheral nerve involvement. In about half of this group of patients, NCSs show slowed MNCVs and prolonged distal latencies consistent with demyelinating neuropathy.

The serum protein electrophoresis shows an IgM monoclonal spike of >3 g/dL, with 75% of these proteins having κ light chain. Reduced IgG and IgA protein titers are often associated. A small monoclonal light chain is detected in the urine of the majority of patients. The diagnosis of WM requires evidence of bone marrow infiltration by lymphoplasmacytoma with the detection of serum IgM monoclonal protein (Table 2). The bone marrow aspirate is hypocellular, but biopsy specimens are hypercellular with infiltration by lymphoplasmacytoid lymphoma with the detection of amyloid. POEMS syndrome is a rare atypical plasma cell proliferative disorder associated with MGUS. Pure sensory polyneuropathy, multiple mononeuropathies and painful predominantly sensory neuropathy with prominent dysautonomia often associated with disordered gait are other clinical presentations. The central nervous system is rarely affected. When IgM binds to MAG or sulfatide, there is an associated increase in the frequency and severity of peripheral nerve involvement. In about half of this group of patients, NCSs show slowed MNCVs and prolonged distal latencies consistent with demyelinating neuropathy.

The reported median survival for WM is approximately 5 years. However, being of an age older than 70, having a hemoglobin level less than 9 g/dL, weight loss, and cryoglobulinemia are adverse predictive factors. Asymptomatic patients without evidence of end organ damage are considered to have smoldering WM and immediate therapy is not required. Anemia or thrombocytopenia and constitutional symptoms related to WM are considered to be indications for therapy. Current treatment options for WM include: rituximab, nucleoside analogues, alkylating agents alone or rituximab in combination with nucleoside analogs, nucleoside analog plus alkylating agents, or combination chemotherapies. Therapy is determined based on the patient’s age and the aggressiveness of the presentation. Since no randomized data exist to determine the best option, patients are preferably treated in clinical trials.

Systemic AL Amyloidosis

Amyloidosis is a multisystem disorder characterized by extracellular deposition of fibrillar proteins that can be deposited in various organs and tissues throughout the body. Diagnosis is based on the recognition of amyloid deposits in the affected organs (Table 4). Amyloid can be detected when tissue is stained with Congo red dye, which displays a characteristic apple green birefringence under polarized light and a characteristic ultrastructural appearance when examined under electron microscopy. The use of the protein composition of the amyloid material has allowed for classification of several distinct types of amyloidosis (Table 4) which
may be localized or systemic. Systemic AL amyloidosis is referred to as primary systemic amyloidosis or primary amyloidosis. AL (Ig light chain) amyloidosis refers to the type of amyloidosis resulting from the amino terminus variable segment of Ig light chain. This variety commonly presents in the absence of a malignant plasma cell dyscrasia, but may occur in association with MM or WM. Although the pathogenesis of AL amyloidosis is poorly understood, one hypothesis involves an uncontrolled expansion of a clone of either malignant or nonproliferative plasma cells that secrete amyloidogenic light chain polypeptides.

AL amyloidosis typically presents with polyneuropathy, autonomic symptoms, and much less often as proximal muscle weakness. Over half of the patients will have systemic organ involvement (nephrotic syndrome, cardiac failure, chronic diarrhea with wasting, hypalbuminemia, cutaneous purpura, macroglossia and hepatomegaly). The clinical prognosis is poor, with about 80% of patients succumbing within 36 months of diagnosis, and about 50% with 12 months. Since mortality is primarily due to cardiac failure, those patients without cardiac and renal involvement have a better prognosis.

Melphalan and prednisone have been the mainstay of therapy with unsatisfactory results. Stem cell transplantation is offered to some eligible patients in addition to novel trials with thalidomide.

### MISCELLANEOUS DISORDERS

#### Lower Motor Neuron Syndromes

Multifocal motor neuropathy (MMN) is another lower MN syndrome associated with increased titers of serum IgM autoantibodies to the ganglioside GM1, and to a lesser extent, other glycolipids. It is distinguished by its characteristic clinical picture, specific electrophysiologic abnormalities, and frequent favorable response to IVIg. Patients typically present with a slowly progressive, predominantly distal asymmetric limb weakness and wasting, primarily in the arms. Deep tendon reflexes may be preserved early in the course of disease. NCSs show evidence of multifocal motor conduction block (defined as a reduction of amplitude of 50% or more at proximal as compared with distal sites of stimulation) in one or more nerves. The disorder is confined to motor axons with sparing of sensory axons. The presence of antiGM1 antibodies is the most typical laboratory finding associated with MMN, although the proportion of affected patients with the antibodies varies from 30 to 80%, and the degree of titer elevation ranges markedly. MMN is a rare condition that affects 1 or 2 persons per 100,000. It occurs more frequently in men than in women, and has a mean age of onset around 40 years of age. The effectiveness of IVIg therapy has been demonstrated in several studies and is widely considered

### Table 4 Classification of Amyloidosis

<table>
<thead>
<tr>
<th>Types of amyloidosis</th>
<th>Major protein Component</th>
<th>Clinical presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL amyloidosis</td>
<td>κ or λ light chains</td>
<td>Primary or localized</td>
</tr>
<tr>
<td>AA amyloidosis</td>
<td>Serum amyloid A protein</td>
<td>Chronic inflammatory conditions; typically acquired but hereditary in case of familial Mediterranean fever; renal presentation most common</td>
</tr>
<tr>
<td>ATTR amyloidosis</td>
<td></td>
<td>Hereditary: peripheral neuropathy and/or cardiomyopathy</td>
</tr>
<tr>
<td>Mutant TTR</td>
<td>Mutated transthyretin</td>
<td>Restrictive cardiomyopathy; carpal tunnel</td>
</tr>
<tr>
<td>Normal TTR (senile amyloidosis)</td>
<td>Normal transthyretin</td>
<td></td>
</tr>
<tr>
<td>B2-microglobulin amyloidosis</td>
<td>B2-microglobulin</td>
<td>Carpal tunnel</td>
</tr>
<tr>
<td>Aβ amyloidosis</td>
<td>Aβ protein precursor</td>
<td>Alzheimer syndrome</td>
</tr>
<tr>
<td>A fibrinogen</td>
<td>Fibrinogen α-chain</td>
<td>Renal presentation</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Lysozyme</td>
<td>Renal presentation most common</td>
</tr>
<tr>
<td>Apolipoprotein A-I</td>
<td>Apolipoprotein A-I</td>
<td>Renal presentation most common</td>
</tr>
</tbody>
</table>

AA = amyloid associated; AL = light chain; Aβ = β amyloid; ATTR = transthyretin

Used with permission from Rajkumar SV, Dispenzieri A, & Kyle RA. (2006).
the gold standard of treatment for MMN.36 It is interesting to note that even after salutary treatment responses, the antiglycolipid levels often remain unchanged. This observation raises questions regarding the pathogenic role these antibodies play in MMN.28

In the mid 1990s, a subset of patients were identified that had purely axonal motor neuropathy with raised anti-GM1 antibody titers, but no conduction block or other features suggesting demyelination and variable response to immunosuppressive therapy. The term multifocal acquired motor axonopathy (MAMA) was proposed for this group of patients.27 An axonal NCS pattern of spontaneous activity and chronic neurogenic in limb muscles normal paraspinal muscle EMG and increased anti-GD1 antibody titers was found in the group responsive to IVlg therapy.27

Because of immunocytochemical studies showing binding of antiganglioside antibodies antigens on MN cell bodies and axons at nodes of Ranvier and motor end-plates, an association between MAMA and MN disease has been questioned. Although cases of high titers of IgM and anti-GM1, ganglioside antibodies have been reported in this disorder, there is little evidence of a causal link.4

Cryoglobulinemia

Proteins (IgG or IgM) that precipitate when cooled then redissolve after warming and circulate as immune complexes in the blood stream are known as cryoglobulins. The Ig may be monoclonal, polyclonal, or both. Cryoglobulinemia is divided into three types based on the composition of the cryoprecipitate: type 1 - isolated monoclonal Igs; type II—a monoclonal mixture of an M-protein and polyclonal Igs (IgG) in the setting of lymphoproliferative disease or hepatitis C; and type III—polyclonal Igs in the setting of a collage vascular or chronic inflammatory disease.3 Cryoglobulinemia classically presents with purpura, arthralgias, asthenia, renal disease, and neuropathy. The disorder has most often been associated with hepatitis C. Less common associations include lymphoproliferative disorders, connective tissue disease, and other chronic infections. PN is reported in 17 to 56% of patients. This neuropathy may appear as either an acute or subacute distal symmetrical or asymmetrical sensorimotor polyneuropathy, or as mononeuropathy multiplex. Sensory symptoms usually precede motor manifestations. Axonal predominates most often, although evidence suggesting demyelination may be present.40

The therapeutic approach to mildly symptomatic cryoglobulinemia consists of conservative measures such as bedrest, avoidance of cold, use of analgesics, and consideration of low dose steroids. For more severe forms complicated by glomerulonephritis, motor neuropathy and systemic vasculitis, plasmapheresis, high-dose steroids and cytotoxic therapy may be warranted. The potential benefits of agents such as melphalan, cyclophosphamide, or chlorambucil must be weighed against the risk of myelodysplastic syndromes or acute leukemia. Interferon has been reported to be of benefit to those with hepatitis C, although a majority relapse 6 months after discontinuation of this agent. While purpuric lesions and liver function abnormalities show a rapid response, the neuropathy and nephropathy are slower to improve. Rituiximab has recently been suggested as an alternative to traditional chemotherapy.5

CONCLUSION

The last two decades have witnessed a growing awareness of the clinical importance of PNs associated with plasma cell dyscrasias. At least 10% of de novo neuropathy patients have an M-protein. Despite the fact that discovery of an associated serious or frankly malignant diseases such as MM, WM, POEMS, lymphoma and AL amyloidosis are uncommon in this group, these individuals require investigation for an underlying cause. The majority are ultimately designated as having MGUS. The evaluation of paraproteinemias includes recognition of the M protein through a variety of biochemical studies and additional testing including a skeletal survey, or aspirated bone marrow biopsy. Because the 25-year risk for progression to myeloma in MGUS is 30%, annual follow up is recommended with measurement of total protein concentration and electrophoresis of serum and urine. While no treatment is indicated for mild or subclinical MGUS, research in the arena of neoplastic plasma cell diseases has lead to new therapies including stem cell transplantation. Innovative research protocols are underway at a number of centers. Recognition of the syndromes associated with monoclonal gammopathies and PN is essential for clinicians caring for these patients, as is familiarity with treatment options which may prove to be beneficial for many selected individuals. A number of recent reviews provided the basis for this summary.43-48

REFERENCES

INTRODUCTION

The various forms of vasculitis make up a heterogenous group of disorders that can affect different organ systems and blood vessel calibers. They frequently affect the peripheral nervous system (PNS). This manuscript will discuss the causes of, and treatment approaches for, the most common forms of vasculitic neuropathy.1

CLASSIFICATION

Classification of the vasculitides has become increasingly sophisticated over the past half-century.2,3 For the neurologist or physiatrist, it helps to conceptualize these classifications by (1) clinical characteristics (systemic or nonsystemic, chronic or acute, or monophasic), and (2) histopathologic features (nerve large arteriole vasculitis or nerve microvasculitis).1 This construct has the limitations inherent in any attempt to divide a continuum into a binary classification scheme. Marked overlap in vessel-size involvement among the various vasculitides must also be considered. Nonetheless, classification based on clinical and histopathologic features has merit. It allows us to characterize an individual’s vasculitic neuropathy in ways that facilitate prognosis, and serve as a blueprint for treatment and management.

Clinically, vasculitis of nerve is either systemic or nonsystemic.1 Systemic conditions are commonly divided into primary systemic vasculitis with no known cause, and secondary systemic vasculitis where a virus, drug, or connective tissue disease is responsible for vessel wall inflammation.4 Vasculitides are further classified by the kind and size of blood vessels and organs involved, disease associations, underlying mechanisms, and sometimes, autoantibody profiles.5 The primary systemic vasculitides most likely to cause vasculitic neuropathy include polyarteritis nodosa (PAN), Wegener’s granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis.2,4,6 Of these, microscopic polyangiitis (MPA) is perhaps the most frequent cause.6

Secondary causes of systemic vasculitis involving peripheral nerves include connective tissue diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus, and Sjögren’s syndrome (SS).7 Mixed, type II cryoglobulinemic vasculitis associated with hepatitis C infection is another secondary form of vasculitis. Other viruses associated with the condition are human immunodeficiency virus (HIV) and cytomegalovirus (CMV). Sarcoidosis affecting nerve may also cause an angiitis.8 The classic name for vasculitis confined to nerve and muscle is nonsystemic vasculitic neuropathy (NSVN).9-13

Unlike NSVN, untreated systemic vasculitic neuropathy (SVN) is often fatal.11 Early on, it may be difficult to distinguish NSVN from SVN; in approximately 10% of cases, what initially appears to be NSVN ultimately becomes systemic vasculitis.10,14 Thus, early phase evaluation should be for SVN. However, some investigators suggest that NSVN is simply part of a continuum in the spectrum of systemic vasculitis. The demonstration of clinicopathologic and pathologic similarities between NSVN and MPA give credence to this view. On the other hand, NSVN and MPA differ in age of onset, severity, and presence of perinuclear neutrophil cytoplasmic antibody (p-ANCA), which is absent in NSVN.12
In terms of peripheral nerve histopathology, nerve vasculitis can be organized into two groups—large arteriole and microvasculitis.\(^{15,1}\) The difference is based on the size of vessels involved, associated diseases, and course and treatment considerations. As before, classification by vessel size is limited by the known overlap of vessel involvement in vasculitis.\(^5\) Large arteriole vasculitis of nerve involves small arteries, large arterioles, and some smaller vessels.\(^{15}\) Almost all nerve vessels are small. Thus, nerve “large arteriole” vasculitis is still a “small vessel” disease; the nerve vessels involved, although small, are larger than those in “nerve microvasculitis.”

Nerve large arteriole vasculitis is usually associated with RA, PAN, Churg-Strauss syndrome, or Wegener’s granulomatosis. Nerve microvasculitis is less well-defined, with vessels that usually include smaller arterioles (ie, <40 pm), microvessels, and venules. It occurs in NSVN, MPA, and immune sensorimotor polyneuropathies sometimes associated with sicca, classical SS, and virus-associated neuropathies (e.g., some cases of HIV, cytomegalic, and hepatitis C).

Many autoimmune, monophasic, or relapsing plexopathies (radiculoplexus neuropathies) should also be classified as nerve microvasculitides. These include diabetic lumbosacral radiculoplexus neuropathy (DLRPN or diabetic amyotrophy), nondiabetic lumbosacral radiculoplexus neuropathy (LRPN), and immune and inherited brachial plexus neuropathies (BPN) (or neuralgic amyotrophy and hereditary neuralgic amyotrophy).

Histopathology of LRPN shows features that suggest nerve microvasculitis. The pathology of BPN (e.g., cervical radiculoplexus neuropathy [RPN]) hasn’t been as well studied as LRPN, but some cases also suggest nerve microvasculitis.\(^{17,18,19}\) RPN doesn’t neatly fit into the “systemic versus nonsystemic” classification scheme. It probably shares more features with NSVN, including vessels of similar size and involvement, primarily confined to nerves (but unexplained weight loss in RPN indicates some effects outside of the PNS). Neither disorder is fatal, but RPN is monophasic and differs from NSVN in the distribution of nerve involvement. In the treatment of RPN (and BPN), the unique temporal profile calls for acute intervention rather than relapse prevention.

**CLINICAL AND DIAGNOSTIC FEATURES OF VASCULITIC NEUROPATHY**

Patients who develop vasculitic neuropathy tend to be over the age of 50.\(^7,20\) The typical clinical features are acute to subacute onset of painful sensory or sensorimotor deficits.\(^{21,22}\) The usual presentations are of an asymmetric polyneuropathy or multiple mononeuropathies (often overlapping).\(^{7,11,16,23-30}\) Commonly, the progression of mononeuropathies is so rapid that the deficits appear confluent. This makes it imperative to question the patient in detail about the clinical course of the initial deficit and all subsequent ones.

Most SVN and NSVN patients experience their first symptoms in the lower extremities, typically the peroneal or tibial divisions of the sciatic nerve, but any nerve can be affected. Vasculitic neuropathy may infrequently present as a distal, symmetric polyneuropathy, which is much less common. Systemic symptoms may include myalgias, arthralgias, weight loss, respiratory symptoms, hematuria, abdominal pain, rash, or night sweats. Early on, these may be minimal or absent.\(^3\) Table 1 lists the clinical characteristics of six common forms of systemic vasculitic neuropathy.

Electrodiagnostic (EDX) studies often reveal characteristic vasculitic neuropathy findings, including acute-to-subacute axonal loss of sensory and motor nerve fibers, often in a patchy, multifocal, or asymmetric pattern.\(^31\) Only conduction slowing or block at common entrapment sites (e.g., median neuropathy at the wrist or peroneal neuropathy across the fibular head) suggest other etiologies, particularly those that increase the likelihood for compression neuropathies. These include some forms of diabetic neuropathies (carpal tunnel syndrome and ulnar neuropathy at the elbow), non-vasculitic RA, or hereditary neuropathy with liability to pressure palsies (HNPP).

Laboratory evaluation of suspected cases of vasculitic neuropathy should almost always include a complete blood count (CBC), metabolic panel (electrolytes, blood urea nitrogen, creatinine, and glucose), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody, rheumatoid factor, PR3/c-ANCA and MPO/p-ANCA, hepatitis B and C panel, and cryoglobulins.\(^{20,1}\) Serum complement determinations are appropriate in suspected mixed cryoglobulinemia or systemic lupus syndromes. In many instances, it is also appropriate to check extractable nuclear antigens, serum angiotensin converting enzyme level, serum protein electrophoresis, and HIV.

Cerebrospinal fluid analysis is usually not helpful, unless the physician is also investigating mimickers, including infectious (e.g., Lyme) or other inflammatory etiologies (e.g., carcinomatous root involvement). Serologic testing is abnormal in SVN; this helps further define the etiology or syndrome (Table 1). In NSVN, the ESR or CRP may be slightly elevated, but other markers of inflammation or systemic disease are usually normal.

Because of the need for long-term treatment with potentially toxic medications, the diagnosis of vasculitis—especially SVN—usually warrants histologic confirmation. One exception might be PAN. It affects larger vessels, and can sometimes be diagnosed with the aid of angiography. In general, the sensitivity of a nerve, or nerve and muscle biopsy, is approximately 60% for vasculitis (if inflammation and vessel wall destruction are mandatory criteria).\(^{29,32}\) Sensitivity of nerve biopsy increases, but specificity decreases if other features, such as ischemic injury (multifocal nerve fiber loss) with inflammation but without vessel wall destruction, are considered sufficient for diagnosis.\(^{26,29,32}\) Some investigators recommend biopsy of both nerve and muscle; for example, the superficial peroneal nerve and ipsilateral peroneus brevis muscle. The sensitivity of a nerve biopsy depends on several factors, including patient selection, which nerve is biopsied, timing
Table 1  A partial list of clinical characteristics and treatments for six common forms of systemic vasculitis affecting small and/or medium-sized vessels of nerve

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Wegener Granulomatosis</th>
<th>Churg-Strauss syndrome</th>
<th>Polyarteritis nodosa</th>
<th>Microscopic polyangiitis</th>
<th>Rheumatoid vasculitis</th>
<th>Mixed cryoglobulinemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral nerve disease</td>
<td>40% – 50%</td>
<td>65% – 80%</td>
<td>35% – 75%</td>
<td>60% – 70%</td>
<td>50% (of cases of rheumatoid vasculitis – a secondary vasculitis that occurs in 5% - 15% of cases of rheumatoid arthritis)</td>
<td>20% - 90%</td>
</tr>
<tr>
<td>Upper airway disease</td>
<td>95%</td>
<td>50% – 60%</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pulmonary disease, radiographic nodule/infiltrates</td>
<td>70% – 85%</td>
<td>40% – 70%</td>
<td>No</td>
<td>15% – 70%</td>
<td>5% - 30%</td>
<td>No</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>70% – 80%</td>
<td>10% – 40%</td>
<td>No</td>
<td>75% – 90%</td>
<td>10% - 25%</td>
<td>33% - 55%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>&lt;5%</td>
<td>30% – 50%</td>
<td>15% – 55%</td>
<td>30%</td>
<td>10% - 30%</td>
<td>&lt; 20%</td>
</tr>
<tr>
<td>Arthralgia/arthritis</td>
<td>60% – 70%</td>
<td>40% – 50%</td>
<td>50% – 75%</td>
<td>40% – 60%</td>
<td>90% - 100%</td>
<td>20% - 90%</td>
</tr>
<tr>
<td>Cardiac</td>
<td>10% – 25%</td>
<td>10% – 40%</td>
<td>5% – 30%</td>
<td>10% – 15%</td>
<td>10% – 30%</td>
<td>No</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>70% – 80%</td>
<td>10% – 40%</td>
<td>No</td>
<td>75% – 90%</td>
<td>10% - 25%</td>
<td>33% - 55%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>&lt;5%</td>
<td>30% – 50%</td>
<td>15% – 55%</td>
<td>30%</td>
<td>10% - 30%</td>
<td>&lt; 20%</td>
</tr>
<tr>
<td>Arthralgia/arthritis</td>
<td>60% – 70%</td>
<td>40% – 50%</td>
<td>50% – 75%</td>
<td>40% – 60%</td>
<td>90% - 100%</td>
<td>20% - 90%</td>
</tr>
<tr>
<td>Cardiac</td>
<td>10% – 25%</td>
<td>10% – 40%</td>
<td>5% – 30%</td>
<td>10% – 15%</td>
<td>10% – 30%</td>
<td>No</td>
</tr>
<tr>
<td>Skin</td>
<td>40% – 50%</td>
<td>50% – 55%</td>
<td>25% – 60%</td>
<td>50% – 65%</td>
<td>30% - 90%</td>
<td>60% - 100% (e.g., palpable purpura)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>5% – 10%</td>
<td>5% – 30%</td>
<td>3% – 30%</td>
<td>10% – 15%</td>
<td>5% - 15%</td>
<td>No</td>
</tr>
<tr>
<td>c-ANCA (PR3)</td>
<td>75% – 90%</td>
<td>3% – 35%</td>
<td>Rare</td>
<td>10% – 50%</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>p-ANCA (MPO)</td>
<td>5% – 20%</td>
<td>2% – 50%</td>
<td>Rare</td>
<td>50% – 80%</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Vessel size involved</td>
<td>small to medium vessels (e.g., capillaries, venules, arterioles, arteries)</td>
<td>small to medium vessels</td>
<td>medium to small arteries (not arterioles, capillaries or venules)</td>
<td>small vessels (e.g., capillaries, arterioles, venules)</td>
<td>Medium to small arteries (histologically indistinguishable from polyarteritis nodosa)</td>
<td>Small (e.g., capillaries, arterioles, venules)</td>
</tr>
<tr>
<td>Other features</td>
<td>asthma, fever, hypereosinophilia</td>
<td>Fever, hypertension</td>
<td>Fever</td>
<td>Elevated serum rheumatoid factor (RF) and ESR, extraarticular disease (e.g., nodules) fever, weight loss, scleritis</td>
<td>Hepatitis C infection, mixed cryoglobulins, fatigue, Raynaud’s phenomenon, leg ulcers, Sicca syndrome</td>
<td></td>
</tr>
<tr>
<td>Viral association?</td>
<td>Sometimes associated with hepatitis B, hepatitis C or HIV. If so, antiviral agent and/or plasmapheresis should be considered.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hepatitis C &gt; 80%</td>
</tr>
</tbody>
</table>

c-ANCA = anti-neutrophil cytoplasmic antibody with cytoplasmic immunofluorescence pattern directed against the neutrophil serine protease proteinase 3 (PR3); ESR = erythrocyte sedimentation rate; HIV = human immunodeficiency virus; p-ANCA = anti-neutrophil cytoplasmic antibody, with perinuclear immunofluorescence pattern, directed against myeloperoxidase (MPO)
in relation to symptoms, and the histologic criteria required for diagnosis.

In large arteriole SVN, pathologic changes are typically found in epineural and perineural vessels 75-200 μm in diameter.11,16 The vessels involved in microvasculitis are usually smaller arterioles without an internal elastic lamina (i.e., < 40 μm), microvessels, and venules. In nerve large arteriole vasculitis, fibrinoid necrosis of the tunica media is often prominent and characteristic. Obvious fibrinoid necrosis is usually not found in nerve microvasculitis, but there is inflammation of the vessel wall, with separation, fragmentation, and necrosis of the thin tunica media.

Both groups of necrotizing vasculitis often show evidence of ischemic injury or repair (i.e., multifocal fiber loss, injury neuroma, neovasculatization, and perineurial thickening). Inflammatory cells separate muscle layers. Muscle leaflets separate with increased severity, becoming fragmented and separated from the microvessel. Obvious occlusion of vessels is not usually seen, but recent or prior bleeding (hemosiderin in macrophages) is typical.

Hemosiderin is typically found adjacent to affected microvessels. Fibrinoid degeneration of the media is almost never observed in microvasculitis, but is common in large arteriole SVN. It can be seen to advantage in Trichrome stain in paraffin sections in nerve large arteriole vasculitis. Angioneogenesis—closely spaced, thin-walled microvessels in regions of previously ischemic areas—is typical of vessel inflammation.

Microvasculitis has been associated with all stages of perineurial injury—from acute fibrinoid degeneration to thickening and scarring and regrowth of microfasciculi through the perineurium into the epineurium (injury neuroma). Segmental demyelination may be found in acute ischemic injury, usually at the borders of ischemic injury, and may relate to axonal atrophy (distal to sites of axonal stasis) or to sites of axonal enlargement. Immune complex deposition in vessel walls is commonly seen in both SVN and NSVN.

**CLINICAL FEATURES OF LUMBROSACRAL AND CERVICAL RPN**

Both diabetic and nondiabetic LRPN are unique forms of vasculitic neuropathy, with stereotypic presentation, relatively confined distribution of nerve injury, frequent weight loss, and monophasic course. Both forms (diabetic and nondiabetic) of LRPN present with acute or subacute pain, followed by weakness in the lower extremities (both proximal and distal segments). Weakness typically starts unilaterally but often spreads to the other lower extremity. Pain is usually severe.

A concomitant thoracic radiculopathy that presents with a band and pain in the abdomen or chest and weakness of abdominal wall musculature is common. A cervicobrachial plexus neuropathy may accompany LRPN in up to 15% of cases, although upper extremity manifestations are greatly overshadowed by the lower extremity neuropathic symptoms, impairments, and disability.33 In contrast to most other cases of NSVN, the LRPNs are monophasic illnesses. Progression lasts weeks or months, and rarely, years; recovery of motor function is slow and incomplete. Although the disorder is more prevalent in diabetes mellitus, glycemic exposure does not appear to be the direct metabolic cause. Frequently associated weight loss may indicate systemic involvement.

Dyck and colleagues17 reported inflammation and microvasculitis in some cases of noninherited and inherited immune BPN (a cervical radiculoplexus neuropathy), but data on the pathologic basis of these conditions are sparse. Some cases of hereditary BPN (also called hereditary neuralgic amyotrophy) are caused by a mutation in the SEPT9 gene.34 Biopsy of a superficial radial nerve during an attack has shown changes that suggest microvasculitis.35

**GENERAL COMMENTS ABOUT TREATMENT**

Assessment of clinical response, especially neuropathic impairment, by neurologists or physiatrists plays an important role in management of vasculitic neuropathy. Reliable endpoints include routine examination of muscle power, deep-tendon reflexes, sensory thresholds, functional rating scores, and EDX testing. Worsening pain is a less reliable endpoint. If new neurological deficits develop in the course of treatment, more aggressive therapy is indicated. Treatment decisions should be made in consultation with a rheumatologist or internist, and based, in part, on the form of systemic vasculitis, extent and degree of organ involvement, prior responsiveness to any treatments, and presence or absence of viral infection. For example, chronic immunosuppressive agents, which may be first-line therapy for nonviral vasculitis, are often relatively contraindicated in viral-associated SVN.

**COMMENTS ABOUT THE TREATMENT OF SVN**

**Vasculitic Neuropathy Not Associated With Virus**

Corticosteroids are usually the initial therapy for nonviral SVN. Treatment strategies to rapidly stop inflammatory damage (induction) are followed by safer long-term suppression (maintenance). Corticosteroids plus an additional immunosuppressant, such as cyclophosphamide, are usually required to treat microscopic polyangiitis or Wegener’s granulomatosis.20,36 In life-threatening cases of PAN and Churg-Strauss syndrome—such as those with cardiac, gastrointestinal, or central nervous system (CNS) involvement—cyclophosphamide should be added. Some Wegener’s granulomatosis or MPA patients will require long-term immunosuppression due to relapsing disease.20,37,38
<table>
<thead>
<tr>
<th>Drug</th>
<th>Partial List of Potential Side Effects</th>
<th>Management of Potential Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>Acute: Increased susceptibility to infections, hyperglycemia, increased appetite and weight gain, anxiety, confusion, insomnia, impaired wound healing, electrolyte disturbances. Chronic: Avascular necrosis of the femoral heads, hyperlipoproteinemia, accelerated atherosclerosis, osteoporosis, myopathy, alteration in fat deposition, peptic ulcer disease, cataracts.</td>
<td>Patients should start or continue an exercise program, monitoring their diet and weight. Blood glucose monitoring periodically during treatment. Bone mineral density testing baseline and annually. Consider bisphosphonates for prophylaxis of steroid-induced osteoporosis (avoid during pregnancy).</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Hemorrhagic cystitis, transitional cell carcinoma of the bladder, oncogenicity, bone marrow suppression, gonadal toxicity, teratogenicity. About one-half of patients will develop hematuria, usually due to cystitis. Dose-related bone marrow suppression is common, with an increased risk of infection associated with leucopenia. Nausea and vomiting. Increased risk of Pneumocystis carinii pneumonia (PCP), especially with combined steroids and cytotoxic therapy. Potential increased risk of other malignancies, including myeloid and lymphoproliferative disorders, years after its discontinuation. Permanent infertility may also occur due to its ability to interfere with spermatogenesis and oogenesis, which is related to its cumulative dose. Teratogenicity may occur.</td>
<td>Hematuria is a sensitive marker for cyclophosphamide-induced bladder injury. Injury is due to acrolein, a toxic metabolite which is excreted into the urine. Shortening the duration of acrolein exposure to the bladder epithelium may minimize the risk of toxicity. Hence, oral administration should be QD, usually in the morning, followed by a large amount of fluids. TCCA, when it develops, almost always does so after episodes of hematuria. Urinalyses q 3 to 6 months, even after discontinuation, as TCCA may develop decades after cyclophosphamide is stopped. In cases of hematuria, discontinuation and referral to a urologist is necessary. CBC with p/ls weekly the first month, then q month while on treatment. Total leukocyte counts below 3500/mL or absolute neutrophil counts below 1500/mL mandate titration or suspension of the drug. Lower neutrophil counts may warrant admission to the hospital and perhaps treatment with broad-spectrum antibiotics. A precipitous drop in cell counts also warrants more aggressive intervention, including cessation of cyclophosphamide. Taking oral cyclophosphamide with or after a meal lessens the likelihood of nausea and vomiting. Consider anti-nausea medications. IV monthly cyclophosphamide also shortens the time patients experience nausea. Patients not allergic to sulfa who are on combination therapy may be treated with “low-dose” oral trimethoprim (160 mg) and sulfamethoxazole (800 mg) TIW. Counseling and birth control measures.</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Bone marrow toxicity</td>
<td>Baseline CBC with platelets should be obtained prior to initiation (usually done as part of VN evaluation) and every three months thereafter. Repeat testing with fever, rash, or mouth ulcers. Baseline LFTs should be obtained prior to initiation of therapy and at least every three months. Repeat testing with fever, rash, or jaundice, especially within the first three months of treatment. Consider other adjuvant therapy in patients with hepatitis or frequent alcohol consumption. Relatively uncommon, but extra caution should be used in patients with baseline renal impairment. A baseline BUN and creatinine is probably sufficient, provided the vasculitis itself does not involve the kidneys. Prophylactic trimethoprim/sulfamethoxazole (160mg/800mg) TIW is recommended. Discontinue the drug in suspected rash secondary to methotrexate. Baseline PFTs in those with rheumatoid vasculopathy may be helpful for comparison if symptoms develop; PFTs not helpful for subclinical detection. Discontinue drug in cases of new or worsening pulmonary function. Consider other adjuvant therapies in patients with seizures. Blood glucose monitoring periodically during treatment. Relatively uncommon, but extra caution should be used in patients with baseline renal impairment. A baseline BUN and creatinine is probably sufficient, provided the vasculitis itself does not involve the kidneys. Prophylactic trimethoprim/sulfamethoxazole (160mg/800mg) TIW is recommended. Discontinue the drug in suspected rash secondary to methotrexate. Baseline PFTs in those with rheumatoid vasculopathy may be helpful for comparison if symptoms develop; PFTs not helpful for subclinical detection. Discontinue drug in cases of new or worsening pulmonary function. Consider other adjuvant therapies in patients with seizures. Bone marrow toxicity Hepatic Fibrosis and cirrhosis; elevated LFT’s Nephrotoxicity Increased risk for opportunistic infections Stevens-Johnson Syndrome, erythema multiforme, and toxic epidermal necrolysis Pulmonary fibrosis (rare) Lowers seizure threshold</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>See table 5</td>
<td>See Table 5</td>
</tr>
</tbody>
</table>

CBC = complete blood count; IV = intravenous; LFT = liver function test; PFT = pulmonary function test; QD = one day; SVN = systemic vasculitic neuropathy; TCCA 1,2,3,4-tetrahydro- -carboline-3-carboxylic acid; TIW = three times a week;
Corticosteroids

In general, corticosteroids, either alone or with other immunosuppressants, remain the first-line therapy for systemic vasculitis (Table 2). Dosage titration should be based on the patient’s disease severity and response to treatment. In severe cases, intravenous methylprednisolone (IVMP) may be appropriate for initial therapy (e.g., 1000 mg IV daily for 3 to 5 days, followed by daily oral prednisone). Daily oral steroids should be continued until the patient has shown a clear response. During the subacute phase of treatment, usually after 6 to 8 weeks, the patient may be transitioned to alternate-day dosing, either at the same or at a lower averaged daily dose. At this time, or after another 1 to 2 months of observation, the physician should begin to taper the steroid dose; for example, by 5-10 mg per day per month, perhaps with lesser decrements occurring near the end of the taper. Table 2 lists the potential adverse effects of steroid therapy.

Immunosuppressant Adjuvant Therapies

The decision to add or withhold a cytotoxic or corticosteroid-sparing agent (e.g., cyclophosphamide, methotrexate, azathioprine, or mycophenolate mofetil) is an important one, preferably made by a rheumatologist or internist with more experience caring for patients with SVN. In general, most experts recommend starting a cytotoxic agent in cases of Wegener’s granulomatosis or microscopic polyangiitis.4,20,37 Cytotoxic agents are also indicated in patients with other forms of systemic vasculitis who progress despite corticosteroid therapy, or who have severe multiorgan involvement, such as pulmonary-renal syndrome, rapidly progressive necrotizing glomerulonephritis, or life-threatening organ or CNS involvement. The physician must keep in mind that adjuvant therapies have a delayed onset of action, often weeks to months. Table 2 lists some of these agents, typical doses, and a partial list of side effects.

Regardless of the treatment, it is important that physicians monitor for, and promptly identify, any life-threatening organ involvement by vasculitis, including the gastrointestinal tract, heart, or CNS.4,38 The involvement of these systems should prompt the physician to add an adjuvant therapy (if not already done) or escalate the doses of existing therapy. However, worsening subjective constitutional symptoms may not reliably signify relapse, so clinical and laboratory parameters must be closely followed. These include a thorough general and neurologic examination and surveillance, CBC, chemistries, ESR, and urinalysis at least every 3 months, with chest radiograph at least annually.38

Cyclophosphamide is an effective drug for induction and for prolonging survival in nonviral systemic vasculitides. Patients usually require between 3 and 12 months of induction therapy before they can be switched to a maintenance immunosuppressant.4,20,36 Oral cyclophosphamide is typically dosed at 2 mg/kg per day. Current data suggest that pulse-dosing cyclophosphamide results in fewer adverse effects, but might be associated with an increased risk for relapse compared to oral cyclophosphamide.23

Methotrexate has been most commonly used for remission maintenance after cyclophosphamide induction.20 A typical approach is to use cyclophosphamide as the adjuvant agent until remission, then switch to methotrexate or azathioprine for maintenance.39

Once the vasculitis is in remission, it is reasonable to continue maintenance therapy for at least a year before attempting to taper the methotrexate or azathioprine. Methotrexate dosing in the range of 15-25 mg once weekly is used for systemic vasculitis.4,36

Azathioprine may be considered for patients unable to tolerate cyclophosphamide therapy.4,20,37,40 It may be as effective as cyclophosphamide in maintaining remission in Wegener’s granulomatosis or microscopic polyangiitis.40 Azathioprine is initially dosed at 50-100 mg or 1 mg/kg p.o., usually divided twice daily. The dose is then increased by 50 mg per day every 4 weeks to a goal dose of 2-2.5 mg/kg/day divided twice daily.

Pilot studies suggest that mycophenolate mofetil and leflunomide can be potentially useful for maintaining remission after cyclophosphamide induction in Wegener’s granulomatosis.20,41,42

Intravenous immunoglobulin (IVIg) has been used in nonvasculitic immune-mediated neuropathies. It generally has a benign safety profile, making it an attractive adjuvant therapy. Small, open label trials of IVIg in SVN suggest clinical benefit.43, 44

Rituximab, a chimeric anti-CD20 antibody, has shown promise in the treatment of cryoglobulinemic vasculitis and RA.45

VASCULITIC NEUROPATHY ASSOCIATED WITH HEPATITIS B or C

It is necessary to determine whether the vasculitic neuropathy is associated with a virus, such as hepatitis B or C, or HIV. A detailed discussion of treatment of viral-associated vasculitis is beyond the scope of this review. A physician experienced in treating viral hepatitis, a hepatologist for example, should make the treatment decisions and manage such patients. In general, chronic immunosuppression is relatively contraindicated in viral-associated vasculitides because such treatment may increase viremia. Shorter courses of immunosuppression, however, are still sometimes employed for PAN associated with hepatitis B. Corticosteroids are typically followed by a longer course of an antiviral agent (either interferon-α2 or the nucleoside analogue, lamivudine), often with concomitant plasma exchange.46-48 Treatment of hepatitis C typically involves pegylated INF-α 2a or 2b, often with ribavirin.49,50

INF-α treatment has been associated with clinical improvement in patients with hepatitis C-cryoglobulinemic vasculitic neuropathy.51-53 The clinician must be aware, however, that exacerbation of vasculitic neuropathy subsequent to initiation of pegIFN-α is an infrequent but widely reported complication of treatment.54,55 In such cases, drug discontinuation may lead to improvement and should be considered. Rituximab may hold promise for treatment of patients with hepatitis C-cryoglobulinemic vasculitic neuropathy.56 Plasma exchange should be considered in fulminant cases.
COMMENTS ABOUT THE TREATMENT OF NSVN, LRPN, AND OTHER RPNs

When considering treatment options for NSVN and RPN, there are a number of things to keep in mind. First, NSVN and RPN are almost always not fatal, and thus, differ from untreated systemic vasculitis. DLRPN and LRPN are usually monophasic, whereas other forms of NSVN are often chronic. Also, neurological deficits seen with NSVN often gradually resolve without treatment, and NSVN disease activity may remit for years, or even decades, before relapsing. Immunosuppressive treatment may not be indicated for NSVN patients with either mild or improving neuropathy. On the other hand, treatment is indicated for more fulminant disease. Patients with active and severe DLRPN or LRPN are often treated with either IVIg or IVMP.

IMMUNOSUPPRESSIVE TREATMENT OF NSVN

Corticosteroids

For cases of NSVN that warrant treatment, oral prednisone therapy is the usual first-line agent. Most experts recommend either 40-60 mg per day or 1 mg/kg/day for 2 to 3 months, followed by steroid taper and transition to alternate-day dosing if the patient has a clinical response. Others, however, think that smaller doses suffice.

Adjuvant Therapies

Based on statistically significant improvements in response rates and disability scores, a relatively recent retrospective study on NSVN (not DLRPN or LRPN) argued for both corticosteroids and cytotoxic adjuvant therapy. However, patients exposed to immunosuppressant therapy also experienced significantly more episodes of pneumonia, varicella zoster, and sepsis. A prospective, randomized trial would be ideal, but seems impractical given the infrequency of NSVN.

Weekly methotrexate is another option in the adjuvant treatment of NSVN. It is probably not necessary to use the higher doses often required in SVN. A starting dose of 7.5 mg by mouth per week, gradually increasing to 15-20 mg per week, is one option.

Azathioprine is another option in the adjuvant therapy of NSVN, one probably better suited for patients with infrequent mononeuropathies. Its therapeutic onset is delayed up to 8 months after initiating therapy; this should be considered when tapering corticosteroids.

TREATMENT OF DLRPN and LRPN

There is no proven course-altering therapy for DLRPN or LRPN, and only one randomized, controlled trial has been done. However, based on anecdotal case reports, patients with DLRPN or LRPN are often treated with IV corticosteroids or IVIg. One noncontrolled study of a series of LRPN patients treated with IV corticosteroids showed that they all improved, many to a marked degree, but the authors warned that the results should be viewed with caution since the monophasic disease improves spontaneously. Treatment should be considered for patients in the acute phase or those in the subacute phase who do not appear to be improving.

This author tends to use IVMP because steroids have been first-line therapy for other forms of microvasculitis. Patients treated with steroids (e.g., DLRPN patients) must be closely monitored for hyperglycemia. A randomized, controlled trial comparing IVMP to IV placebo in DLRPN has been completed, but all of the data have yet to be analyzed.

Summary

The various forms of vasculitis affect different organ systems and blood vessel calibers. Classification of the vasculitides has become sophisticated and treatment options vary depending on the classification.

REFERENCES


Multifocal Dysimmune Demyelinating Neuropathies

Richard A. Lewis, MD
Professor and Associate Chairman
Department of Neurology
Wayne State University School of Medicine
Detroit, Michigan

INTRODUCTION

Multifocal motor neuropathy (MMN) and multifocal sensorimotor demyelinating neuropathy (MSMDN) with persistent conduction block (CB) are two immune-mediated disorders that present as multifocal dysimmune demyelinating neuropathies (mononeuropathy multiplex). The term Lewis-Sumner syndrome (L-SS) has been used interchangeably to describe both conditions.

MMN is a variant of chronic immune-mediated demyelinating polyneuropathies, while L-SS falls under the category of “classic” chronic inflammatory demyelinating polyneuropathy (CIDP) (Table 1). This manuscript considers MMN and L-SS separately, using the latter to describe only the sensorimotor disorder. It reviews CB, then discusses clinical, electrodiagnostic (EDX), and laboratory features of the two conditions, as well as treatments.

MONONEUROPATHY MULTIPLEX

A 1982 landmark report in five patients with sensorimotor mononeuropathy multiplex found not only Wallerian degeneration—the expected outcome in vasculitic mononeuritis multiplex—but striking and persistent multifocal CB and segmental demyelination. Two patients treated with prednisone responded in a time frame consistent with recovery from CB rather than the slower course of recovery from Wallerian degeneration.

In contrast, two reports in 1988 found that patients thought to have lower motor neuron (LMN) forms of amyotrophic lateral sclerosis (ALS) actually had a pure motor mononeuropathy multiplex related to CB. Since then, a number of studies have described patients with MMN and MSMDN (or L-SS).

Whether those with MMN and MSMDN (L-SS) have the same disorder with varying degrees of sensory involvement has been debated. Recent reports suggest significant differences between these two disorders; differences that might have important therapeutic and pathophysiologic significance.

CONDUCTION BLOCK

CB is the defining feature of both MMN and L-SS. The term describes the physiologic phenomenon in which saltatory conduction is stopped but the axon remains intact. This is in contrast to conduction failure, where conduction is lost due to Wallerian degeneration.

CB is synonymous with the term neurapraxia, which is part of the classic Seddon classification of nerve injury. Segmental demyelination can cause CB. This is apparent when current leakage from internodal myelin reduces the driving current to activate subsequent nodes of Ranvier. However, data show that it only takes paranodal retraction to produce CB. This has a profound effect on capacitance in the region to an extent that can explain the CB.

The understanding of the structure of the nodal, paranodal, juxtaparanodal, and internodal regions has become more sophisticated in the past few years. In myelinated nerve fibers, the fast potassium channels in the juxtaparanodal region are normally inactive, but become activated when there is paranodal retraction. This shortens the duration of the action potential and reduces the driving current, potentially leading to CB at the next node. Other aspects of maintaining the resting membrane potential are crucial to understanding normal nerve function and what happens under pathologic conditions.
CB can occur with segmental demyelination, paranodal retraction, and other disorders of the Schwann cell and myelin. It can also occur without any myelin change. The CB due to local anesthetics, such as lidocaine, and acute motor axonal neuropathy (AMAN) are two examples. This may be particularly relevant to MMN, which has many parallels to AMAN.

The prognosis for return of function after CB is considered very good no matter what the cause. Saida and colleagues studied the time course for restoration of conduction by following physiologic and pathologic changes after intraneural injection of immune sera. The injection caused CB within 60 minutes and segmental demyelination within 24 hours. Remyelination started by day eight, and by day 10, conduction began to be restored coincident with 2 to 8 myelin wraps around the axon. At 37 days, myelin thickness was about one-third of controls, and conduction velocity was almost normal. Thus, it takes only a few wraps of myelin to restore conduction to a nerve fiber, and normal conduction does not require full myelin thickness.

**CLINICAL DETERMINATION OF CB**

CB is a physiologic finding of individual nerve fibers, but clinical nerve conduction testing is performed on whole nerve trunks comprised of hundreds to thousands of nerve fibers. Nerve conduction studies determine what is happening to individual nerve fibers based on observations on a population of fibers. To determine CB, the amplitude on proximal stimulation is compared to that on distal stimulation. When a normal reduction in amplitude on proximal stimulation occurs due to temporal dispersion and phase cancellation, most nerves do not have all fibers undergoing block. Some may be spared, and some may have Wallerian degeneration. Proximal stimulation that produces reduced but not absent response is known as partial conduction block.

A number of pitfalls in determining CB include submaximal stimulus proximally, excessive stimulus distally, and failure to recognize anatomic variations. Many criteria have been established to determine CB. The range of amplitude/area reductions on proximal stimulation compared to distal range from 20-50%. The shorter the segment of nerve studied, the smaller the reduction of amplitude needed to determine CB. Thus, a 20% reduction of amplitude over 10 cm rather than 40 cm is more likely to accurately reflect block. Many attempts have been made to standardize criteria. In general, the lower the amplitude drop required to determine CB, the more sensitive and less specific the criteria are likely to be. Many authors, particularly for research purposes, recommend criteria of approximately 50% reduction in both amplitude and area to determine CB with less than 20% increase in duration.

Clinical improvement of function in most disorders in which CB plays a role, such as Guillain-Barré syndrome (GBS) and acute compressive neuropathies, follows the time course of conduction restoration seen in experimental models. However, in MMN and L-SS, CB can persist for months and even years. The reasons for this remain unclear, but recent studies of axonal excitability are shedding light on the nodal and paranodal changes in these disorders, and may eventually explain why CB can persist for so long. This unique aspect of MNN and L-SS warrants particular attention.

**MULTIFOCAL SENSORIMOTOR DEMYELINATING NEUROPATHY (L-SS)**

Prior to the 1982 report by Lewis, Sumner, Brown and Asbury, only CIDP and the demyelinating neuropathy associated with multiple myeloma were considered chronic immune-mediated demyelinating neuropathies. Currently, there are over 10 different disorders that fall under this heading (Table 2).

CIDP remains the prototypic chronic immune-mediated neuropathy. It is characterized by greater weakness than sensory loss involving symmetric proximal and distal regions. The patients in the 1982 report had a sensorimotor mononeuropathy; MADSAM

### Table 1 Chronic Immune-Mediated Demyelinating Polyneuropathies (CIMDP)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIDP (Chronic Inflammatory Demyelinating Polyneuropathy)</td>
<td></td>
</tr>
<tr>
<td>CIDP Variants</td>
<td></td>
</tr>
<tr>
<td>Sensory Predominant</td>
<td></td>
</tr>
<tr>
<td>Associated with multiple myeloma</td>
<td></td>
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<tr>
<td>Associated with Paraprotein</td>
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<tr>
<td>IgA and IgG</td>
<td></td>
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<tr>
<td>Associated with CNS demyelination</td>
<td></td>
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<tr>
<td>Associated with systemic disorders</td>
<td></td>
</tr>
<tr>
<td>Multifocal Sensorimotor Demyelinating Polyneuropathy with persistent conduction block (Lewis-Sumner Syndrome; MADSAM)</td>
<td></td>
</tr>
<tr>
<td>CIMDP</td>
<td></td>
</tr>
<tr>
<td>Distinct from CIDP</td>
<td></td>
</tr>
<tr>
<td>Polynoemopathy Organomegaly Endocrinopathy M-Proteins Skin (POEMS) Demyelinating Neuropathies Associated with IgM MGUS</td>
<td></td>
</tr>
<tr>
<td>With anti-MAG antibodies</td>
<td></td>
</tr>
<tr>
<td>Without anti-MAG</td>
<td></td>
</tr>
<tr>
<td>Chronic Ataxic Neuropathy Ophthalmoplegia M-protein Agglutination Disialoglycans antibodies (CANOMAD)</td>
<td></td>
</tr>
<tr>
<td>Multifocal Motor Neuropathy (MMN) with persistent conduction block</td>
<td></td>
</tr>
</tbody>
</table>

Anti-MAG = anti-myelin associated glycoprotein; CNS = central nervous system; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; MADSAM = multifocal acquired demyelinating sensory and motor polyneuropathy; MGUS = monoclonal gammopathy of undetermined significance.
finding of a demyelinating mononeuropathy multiplex and the persistent CB. These patients had MSMDN, a variant of CIDP that had previously been described as a symmetric disorder.

The naming of MSMDN has been controversial. L-SS has been used by many authors and speakers. Saperstein and colleagues17 suggested MADSAM, the initials of Multifocal Acquired Demyelinating Sensory and Motor neuropathy. Van den Berg-Vos and colleagues have suggested “multifocal inflammatory demyelinating neuropathy.”18 This is only slightly less awkward than the original title,1 and does not truly separate MSMDN from MMN. In this manuscript, L-SS will be the preferred name for MSMDN.

CLINICAL FEATURES

The five patients in the 1982 report1 had symptoms that included pain and numbness as well as weakness in multiple nerve distributions. Motor neuron disease was not considered in the differential diagnosis of any of these patients. Two of them had episodes of optic neuritis with central scotomas, afferent pupillary defects, and prolonged visual evoked responses. Cerebrospinal fluid (CSF) protein was normal or mildly increased. Sural biopsy revealed segmental demyelination and a small amount of inflammatory cell infiltrate. Two patients treated with corticosteroids improved.

Since then, well over 100 patients described in the literature have had the same clinical features. They presented with sensorimotor symptoms, frequently with neuropathic pain, in the distribution of individual nerves—a true mononeuropathy multiplex. When severe, mononeuropathies become confluent, and individual nerve abnormalities may not be detectable with examination. How frequently this happens in L-SS is unclear; some authors have labeled disorders in CIDP patients with the varying degrees of asymmetry as L-SS. But in this author’s experience, L-SS tends to stay strikingly multifocal, and labeling asymmetric but generalized CIDP as L-SS may cause confusion.

Studies describe cranial nerve abnormalities, including facial, trigeminal, and hypoglossal nerve palsies. Central nervous system abnormalities have been mentioned, but not as commonly as one would expect given the two patients with optic neuropathy in the original 1982 cohort.1 Tinel signs at sites of CB are common. No predisposing factors are known, but L-SS has been seen in patients with hepatitis B and/or C, with treatment with etanercept or infliximab associated with CIDP. A number of reports of L-SS or MMN with infliximab raise the question of whether these multifocal disorders are seen, in particular, with this tumor necrosis factor-alpha monoclonal antibody. If true, this may be a clue as to the restricted nature of these disorders.

CSF protein is normal or mildly increased, usually less than 100 mg. This is consistent with the idea that the disorder does not have a predilection for the nerve roots. There are no specific laboratory abnormalities. In particular, antibodies to ganglioside (anti-GM1) and other anti-ganglioside antibodies are not usually detected, or are found in low titers. To this author’s knowledge, no L-SS patient has had strikingly high anti-GM1 antibodies.

EDX findings in L-SS are similar to those in CIDP; although more nerve segments are normal. The multifocal aspect of L-SS is more striking than that of CIDP, and the partial motor CB is a more prominent feature. Nerve biopsies have shown evidence of segmental demyelination and inflammatory infiltrates.

Treatment of L-SS has also mirrored that of CIDP. Intravenous immunoglobulin (IVIg), plasmapheresis, and corticosteroids are all effective in a majority of patients, but no single therapy has been found to benefit all.

Table 2  Mononeuropathy Multiplex

<table>
<thead>
<tr>
<th>Demyelinating Neuropathies</th>
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<tr>
<td>Multifocal Motor Neuropathy with Persistent Conduction Block</td>
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<tr>
<td>Multifocal Sensorimotor Demyelinating Neuropathy with Persistent Conduction Block (Lewis-Sumner Syndrome)</td>
</tr>
<tr>
<td>Hereditary Neuropathy with Predisposition to Pressure Palsies</td>
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<tr>
<td>Vasculitic and Ischemic Neuropathies</td>
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<tr>
<td>Systemic Lupus Erythematosus</td>
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<tr>
<td>Rheumatoid Vasculitis</td>
</tr>
<tr>
<td>Systemic sclerosis (Scleroderma)</td>
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<tr>
<td>Periarthritis Nodosa</td>
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<tr>
<td>Churg-Strauss</td>
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<tr>
<td>Wegener’s Granulomatosis</td>
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<tr>
<td>Paraneoplastic vasculitic neuropathy</td>
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<td>Nonsystemic vasculitic neuropathy</td>
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<td>Behçet Syndrome</td>
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<tr>
<td>Giant Cell Arteritis</td>
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<td>Diabetes mellitus</td>
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<tr>
<td>Lumbosacral Radiculoplexopathy</td>
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<tr>
<td>Truncal Radiculopathy</td>
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<td>Cranial Mononeuropathies</td>
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<tr>
<td>Sensory Perineuritis</td>
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<td>Infectious Neuropathies</td>
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<tr>
<td>Leprosy</td>
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<tr>
<td>Herpes Zoster</td>
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<tr>
<td>Lyme Disease</td>
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<tr>
<td>HIV associated cytomegalovirus</td>
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<td>Hepatitis C and cryoglobulinemia</td>
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<tr>
<td>Other causes</td>
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<tr>
<td>Sarcoid</td>
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<tr>
<td>Brachial Neuritis (Parsonage-Turner Syndrome)</td>
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<tr>
<td>Monomelic Amyotrophy</td>
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<tr>
<td>Malignant infiltration of peripheral nerve</td>
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<tr>
<td>Neurofibromatosis</td>
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</tbody>
</table>

HIV = human immunodeficiency virus
Both L-SS and CIDP are sensorimotor demyelinating neuropathies evidenced by electrophysiology and pathology. Neither disorder has been clearly associated with a specific antigen-antibody, and their pathophysiologies remain unclear. The disorders have a similar response to immunosuppression or immunomodulation. Therefore, it is reasonable to consider L-SS a multifocal variant of CIDP.

**MMN WITH PERSISTENT CB**

**Background**

Two landmark reports in 1988 by Parry and Clarke and Pestronk and colleagues identified MMN. However, various aspects of the disorder were described in other studies that preceded these. The 1988 patients were initially diagnosed with LMN forms of ALS, but were later found to have a multifocal neuropathy. All patients in the two studies (five in Parry and Clarke and two in Pestronk and colleagues) presented with multifocal weakness, atrophy, cramps, and fasciculations without significant sensory complaints. Symptoms began in the arms, reflexes were usually normal or lost focally, CSF protein was normal or minimally increased, and the course was slowly progressive. Treatment responses varied. Two patients had a poor response to plasmapheresis or prednisone; the others had mixed results with cyclophosphamide.

Cardinal features of the disorder were multifocal CB and slowing confined to motor nerve fibers. Distal sensory responses were normal, as were somatosensory evoked potentials (SEPs) and compound nerve action potentials across the regions of motor block. Sural nerve biopsies in the two Pestronk and colleagues cases were normal in one patient and showed mild Wallerian-like degeneration in the other. A motor point biopsy showed axonal loss and demyelination of the remaining axons. Both of the patients had IgM antibodies that reacted with GM1 ganglioside. The titers of the anti-GM1 antibodies fell after cyclophosphamide treatment. Both reports mention that some of the patients had mild and vague sensory symptoms, but no significant abnormality on clinical examination. Sensory conduction studies were normal.

Since these studies, a number of case reports and small series have defined the clinical syndrome and the electrophysiological features. They have addressed the controversial issue of the significance of elevated titers of anti-GM1 antibody and response to various treatments. In particular, many authors have emphasized IVIg and/or cyclophosphamide in the treatment of MMN.

**CLINICAL FEATURES**

MMN is a very rare motor disorder affecting no more than 1 person per 100,000, and is more common in men than women, with at least a 2:1 ratio. Age of onset is between 20 and 70 years, with most patients between 25 and 55 years of age. The disease usually progresses slowly, with some reports indicating a course of over 20 years. However, more aggressive cases have been reported.

Patients may be misdiagnosed with an LMN form of ALS. They present with usually painless, asymmetric weakness, atrophy, and fasciculations of the upper extremities; the distribution may be isolated to one or two nerves. While the legs may become involved, they are rarely the first limbs to do so. The disease is usually less severe in the legs. Patient may remain ambulatory despite severe upper extremity weakness.

The degree of sensory involvement is controversial. Many patients describe vague sensory phenomena or intermittent mild sensory symptoms, but there are no discrete sensory symptoms in the distribution of the motor abnormalities. Sensory examination is almost always normal, even in patients with symptoms. However, some reports mention distal vibration sense reduction or sensory symptoms later in the course of the disease. Recent studies describe development of electrophysiologic sensory abnormalities over time. MMN seems to affect predominantly motor nerve fibers, but some sensory nerves may become damaged over time or with severe disease. In a nerve with both motor and sensory fibers, motor disorder should be strikingly more severe than sensory disorder.

Atrophy, fasciculations, myokymia, and cramps are seen in various combinations. Tinel signs at the sites of the CB have not been mentioned. Studies describe focal hemiatrophy of the tongue, but bulbar and pseudobulbar dysfunction have not been reported. Deep tendon reflexes tend to be preserved out of proportion to the weakness. They can be lost focally, particularly in the arms, but it is unusual to have complete areflexia unless the weakness becomes generalized and profound.

Some reports mention relative hyperreflexia, but Babinski responses or sustained clonus pointing to upper motor neuron (UMN) involvement have not been seen. A study in 69 patients with motor neuron disease assessed whether UMN signs can clinically distinguish ALS from MMN. Seventeen patients had either motor CB (10 patients) or focal temporal dispersion (7 patients). Findings suggest that the patients with temporal dispersion were more likely to have UMN signs, and that partial motor CB (PMCB) may distinguish MMN from ALS. The authors also noted that the diagnosis of MMN should be questioned in patients with otherwise unexplained UMN signs.

**EDX FEATURES**

While CB is the defining EDX feature of MMN, other EDX features of segmental demyelination have been noted. In most of these studies, strict criteria for MMN (compared to L-SS) were not clear. Other demyelinating features described included prolonged distal motor and F-wave latencies, multifocally slow motor conduction velocities, and temporal dispersion. In most instances, CB was detected in at least one nerve, along with the other features of demyelination.

These findings may be in nerves without CB. Whether the diagnosis of MMN can be made without evidence of CB remains controversial. Most criteria for the diagnosis of MMN require
PMCB and a pure motor disorder.\textsuperscript{31,01} However, some reports suggest that patients with otherwise typical MMN, but without PMCB, have similar clinical findings and response to IVIg.\textsuperscript{18}

Earlier studies found response to treatment was not as good in patients without block compared to those with CB.\textsuperscript{32-34} Virtually all MMN diagnostic criteria published to date require PMCB in at least two nerves. Still, questions remain on whether there is any difference between MMN with PMCB and MMN without it.

A number of reasons explain why CB may not be detected. Most lesions that cause PMCB have some degree of associated axonal loss. If severe, CB in other nerve fibers may not be detected. Depending on the duration and severity of the illness, PMCB lesions may evolve into axonal loss. In addition, PMCB in a segment of nerve that cannot be easily tested may be missed. In patients with an appropriate clinical picture and EDX evidence of segmental demyelination (but without CB), it is it is reasonable to strongly consider MMN.

Electrophysiologic findings also raise other questions. Are the nerve lesions of MMN due to primary demyelination or a primary disorder of the nodal and axolemmal membrane? It is not clear in MMN, as opposed to L-SS, whether other EDX signs of demyelination are prominent in regions without block.

Pathologic findings of segmental demyelination are also not prominent. Data show that sural nerve biopsies are usually normal and fascicular biopsies at the site of PMCB do not consistently demonstrate demyelination.\textsuperscript{35,36}

Sensory conduction studies are normal in MMN. Investigations into sensory conduction changes in the regions of motor block have yet to detect any abnormality in compound nerve action potentials and SEPs.\textsuperscript{2,26,27,35}

LABORATORY FEATURES

CSF protein is normal or mildly elevated in MMN,\textsuperscript{17} reflecting the minimal involvement of nerve roots. No other significant abnormalities appear on routine spinal fluid or serum testing.

Elevated titers of antibody against GM1 ganglioside are the most significant, albeit controversial, laboratory finding in MMN. GM1 is one of a number of gangliosides, or constituents of cell membranes, that have been implicated in neuroimmunologic disorders. The GM1 epitope is present in motor neurons and their axons, and to a lesser extent in dorsal root ganglion cells and sensory axons,\textsuperscript{37} but there may be differences in the ceramide composition of GM1 in motor and sensory axons.\textsuperscript{38}

While the amount of GM1 in peripheral nerves is minimal, it is a major peripheral nerve antigen found at nodes of Ranvier and on the axolemma.\textsuperscript{39} The mechanisms by which anti-GM1 antibodies might cause CB remain unclear. The possibility that they cause blockade of sodium channels\textsuperscript{40} has been challenged.\textsuperscript{37} An alternate explanation of nerve fiber membrane hyperpolarization mediated by potassium channels has been suggested as a mechanism of increasing nodal threshold to the point of producing CB.

The incidence of anti-GM1 antibodies in MMN varies from 20-80%. The discrepancy is multifactorial. It is unclear how high titers must be to be considered significant, but specificity only increases with very high titers. Analytic techniques vary among laboratories, and not all labs use the same disease controls. This makes it difficult to compare results from different laboratories.

Pestronk and Choksi\textsuperscript{41} found that 85% of patients with MMN had elevated titers of GM1 combined with other lipids, including galactocerebroside and cholesterol, while none with ALS did. However, Carpo and colleagues,\textsuperscript{42} using the same technique, noted elevated titers in only 35% of patients with MMN. Thus, the sensitivity of IgM anti-GM1 antibodies remains variable, and possibly laboratory-dependent.

Specificity has also been variable, but most of the recent studies have found high titers primarily in MMN, and very rarely in ALS, CIDP, or other neurologic disorders. However, because MMN is rare compared to ALS, the predictive value of high GM1 titers is unclear. At best, they may support the diagnosis of MMN when clinical and/or electrophysiologic findings are unclear.\textsuperscript{43}

Thus, current data point to a correlation between high-titer anti-GM1 antibodies and MMN. High titer antibodies in patients with other diagnoses might encourage clinicians to reevaluate the situation and reconsider MMN. On occasion, the detection of high titer antibody may suggest an empirical trial of immunotherapy in a patient with an otherwise untreatable condition. It may be very difficult for a physician not to consider IVIg in a patient with possible or probable ALS who also has high titers of anti-GM1 antibodies.

A number of investigations\textsuperscript{32-34} have found no response to treatment in patients with LMN disorders (LMND) without block. One report,\textsuperscript{44} on the other hand, noted improvement with plasmapheresis and cyclophosphamide in four patients with LMND and high titer anti-GM1 antibodies without CB. While it is enticing to consider immunomodulating and/or immunosuppressant treatment in atypical cases of LMND, experience to date suggests that one cannot be overly optimistic about success.

Anti-GM1 antibodies appear to have limited utility as a routine diagnostic tool. In patients with typical clinical presentation and electrophysiologic abnormalities, the presence or absence of anti-GM1 antibodies does not add to diagnostic specificity nor does it help predict who will respond to therapy. The one situation where it might be helpful (and this requires further study) is in patients with a LMN syndrome without CB. In this unusual situation, the presence of IgM anti-GM1 antibodies may suggest that the patient has MMN and might respond to therapy.

Thus, the diagnosis of MMN depends on the combination of clinical findings. These include weakness without sensory loss or
been documented. Alternative treatments with documented regions of CB or progressive axonal loss during treatment have been noted, although it is difficult to understand how strength discrepancy between clinical and electrophysiologic improvement studies frequently show at least partial reversal of the CB. Some testing and functional assessments may be helpful. Repeat EDX It is important to monitor treatment carefully. Quantitative muscle function. This approach minimizes the cost and inconvenience to the patient without compromising clinical status. Determining whether treatment is effective requires realistic expectations on the part of physician and patient. If new symptoms and signs occur after a full course of treatment, it is unlikely that IVIg is going to be beneficial. But lack of improvement may not mean treatment failure. Muscle with severe atrophy and denervation may not have the capability of recovery. Most clinicians would treat for 6 to 12 weeks. It may not be necessary to treat every patient with MMN. With greater recognition of this disorder, patients are being diagnosed earlier and some may have very few lesions and minimal functional deficit. In addition, the disorder may be very slow and intermittent, with long periods of inactivity. In these instances, it may be prudent to withhold treatment until active CB lesions develop or functional disability occurs. It is important to monitor treatment carefully. Quantitative muscle testing and functional assessments may be helpful. Repeat EDX studies frequently show at least partial reversal of the CB. Some discrepancy between clinical and electrophysiologic improvement has been noted, although it is difficult to understand how strength could improve without CB doing so as well. Unfortunately, not all patients benefit from IVIg, and new regions of CB or progressive axonal loss during treatment have been documented. Alternative treatments with documented benefit are relatively few. Both oral and high dose intravenous corticosteroid treatment have been remarkably ineffective. The few reports using plasmapheresis without other medications have not been encouraging either. Cyclophosphamide is the only immunosuppressant proven effective. There is no consensus on optimal treatment. Nobile-Orazio and colleagues used relatively low-dose (1.5-3 mg/kg/d) oral cyclophosphamide in 2 patients and felt that the frequency of IVIg treatments could be reduced. In a review article without published data, recommended 6 monthly treatments at 1 gm/m2 preceded by 2 plasma exchanges. This approach reduced the serum anti-GM1 titer in 60-80% of patients, with functional benefit in some of them. He found remission of 1 to 3 years, but relapse frequently occurred, with potential need for retreatment. The risks of cyclophosphamide include bone marrow suppression, risk of opportunistic infection, and increased risk of neoplasia. It is important to determine whether the possible benefits outweigh the risks of cyclophosphamide treatment. Recently, there has been interest in the possible efficacy of rituximab, a monoclonal antibody directed against the CD20 antigen on the surface of β-cells. Originally used as a treatment against β-cell lymphomas, this intravenous therapy depletes the β-cells that produce the immunoglobulins. It has therefore been considered for neuropathies associated with IgM monoclonal gammopathies, including MMN. Reports have been encouraging on the use of rituximab in IgM-related neuropathies, and some patients with MMN have seemed to respond. But the response has not been robust, and several recent series have been discouraging. More effective and long lasting therapies are needed for MMN. These will require investigation in multicenter randomized controlled trials. MMN VERSUS L-SS Prior to 1995, L-SS was mostly either ignored or lumped with MMN. But recently, there have been a few more series of patients with sensorimotor symptoms. These reports, consistent with the 1982 cohort,1 suggest differences between patients with pure motor symptoms and those with sensory and motor symptoms (Table 3). The increased incidence of MMN in males is not seen in L-SS. Pain, paresthesias, and Tinel signs are only seen in patients with sensory symptoms. High titers of GM1 antibodies have not been reported in LSS, although noted 1 patient out of 16 with mildly elevated titers. CSF protein, while not very elevated, tended to be higher than in patients with MMN, suggesting that nerve roots may be more involved in L-SS. A significant number of patients with L-SS respond to corticosteroids; 50% (3 of 6) in Saperstein and colleagues’ series,17 and 79% (11 of 14) in Oh and colleagues report. This is in contrast to patients with MMN, in whom corticosteroids have no effect. Most patients
with MMN who respond to corticosteroids have sensory signs or symptoms, and on closer view, are more likely to have L-SS.

The motor CBs in L-SS are indistinguishable from those in MMN, but whether there are changes in segmental demyelination is less clear. Are distal latencies, temporal dispersion seen in regions outside the block, in both disorders? Unlike MMN, which shows normal sensory conduction through areas of motor block, there is now at least one case of L-SS demonstrating sensory CB that improved with treatment.61

Sural nerve biopsies of patients with L-SS reveal significantly more abnormalities consistent with a demyelinating neuropathy than do those of patients with MMN.62 Fascicular biopsies at the site of CB appear to be different in the two disorders. In L-SS, segmental demyelination and inflammatory cell infiltrates are prominent, but in at least one report in MMN, no inflammation was seen and limited abnormalities of myelin were noted.36 If these findings are confirmed, it would suggest that MMN is a disorder of the axon and node of Ranvier, a chronic version of AMAN, whereas L-SS is a CIDP variant. This would explain the difference in treatment response to corticosteroids.

Some patients fall into a “gray zone” where they cannot be easily labeled as having MMN or L-SS. Reports show some who present with a pure motor syndrome but then develop sensory symptoms years later.62 Some patients have a few sensory symptoms or minor changes on sensory conduction studies, and it becomes difficult to decide whether these changes are significant enough to warrant a diagnosis of L-SS.

These are reasons why some investigators suggest “lumping” MMN and MSMDN together as a single entity. To find out if the distinctions mentioned above are significant, it will be necessary to identify more patients with both MMN and L-SS. Until then, it seems prudent to separate the two disorders.

Combining the two disorders might confuse the issue of GM1 antibodies. The true incidence of these in MMN will never be known if patients with L-SS are included in studies. More importantly, the response to corticosteroid therapy differs radically. The potential benefits of long-term prednisone in L-SS may outweigh the risks.

However, there is currently no evidence on which to base the use of corticosteroids in MMN, and growing evidence to suggest that corticosteroids may exacerbate the disease.

**SUMMARY**

L-SS is a demyelinating neuropathy that is a mononeuropathy multiplex variant of CIDP. MMN is a disorder that may be considered the chronic form of L-SS, with similar physiology, laboratory features, and possibly pathology. Despite some overlap, L-SS and MMN appear to be pathophysiologically distinct entities with persistent CB in common.

**NOTES**

Aspects of this manuscript have been published previously.


**REFERENCES**


