Basics With the Experts

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Basics With the Experts

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Chair: Peter D. Donofrio, MD

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Objectives

Objectives - Participants will acquire skills to (1) Diagnose and assess radiculopathies using EMG, (2) test the median and ulnar nerves using NCS, (3) diagnose patients with weakness using EDX studies, and (4) assess patients with a polyneuropathy using the clinical presentation, laboratory assessment, and EDX testing.

Target Audience:
- Neurologists, physical medicine and rehabilitation and other physicians interested in neuromuscular and electrodiagnostic medicine
- Health care professionals involved in the diagnosis and management of patients with neuromuscular diseases
- Researchers who are actively involved in the neuromuscular and/or electrodiagnostic research

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Basics With the Experts

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Dr. Dillingham attended the University of Washington in Seattle, where he earned his medical degree, and then completed his internship and residency in rehabilitation medicine. Following his training, Dr. Dillingham served for four years in the United States Army at Walter Reed Army Medical Center, in Washington, D.C. Upon completing his military service, Dr. Dillingham joined the Department of PM&R at the Johns Hopkins University. In 2003, he assumed the chairmanship of the Department of Physical Medicine and Rehabilitation at the Medical College of Wisconsin. He is currently the William J. Erdman II, professor and chair for the Department of Physical Medicine and Rehabilitation (PM&R) at the University of Pennsylvania in Philadelphia, and the chief medical officer for the Pennsylvania Institute for Rehabilitation Medicine. Dr. Dillingham is board certified in PM&R as well as electrodiagnostic medicine. His research interests have encompassed prosthetic engineering, health services use and outcomes, and electrodiagnostic medicine. Dr. Dillingham has been active in the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) for more than 20 years. Dr. Dillingham served as president of the AANEM from 2010 to 2011, and in 2010 received the AANEM Distinguished Researcher Award.

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Dr. Stolp received her medical degree from the University of Minnesota. She trained in physical medicine and rehabilitation (PM&R) residency followed by a fellowship in neuromuscular disease and electromyography at the University of Michigan. She also received a Master of Science degree in clinical research design and experimental analysis from the University of Michigan’s School of Public Health. She is associate professor of PM&R, and has been at Mayo Clinic Rochester since 1991 with a joint appointment in the departments of PM&R and neurology. She is presently the medical director for the Doctorate in Physical Therapy Program, Mayo School of Health Sciences. She is currently president of the Association of Academic Physiatrists (AAP). She is a former president of the American Association of Neuromuscular & Electrodiagnostic Medicine and is currently treasurer of the American Board of Electrodiagnostic Medicine. Her research interests include healthcare costs for the disabled, spasticity management, and neuromuscular disease.

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Dr. Donofrio is a graduate of The Ohio State University School of Medicine. He completed an internal medicine residency at Good Samaritan Hospital in Cincinnati, OH, and a neurology residency and neuromuscular fellowship at the University of Michigan. After several years on the faculty at the University of Michigan, he moved to Wake Forest University where he remained for 20 years before moving to Vanderbilt University Medical Center. He is professor of neurology and chief of the neuromuscular section, the EMG laboratory, the Muscular Dystrophy Association Clinic, and the Amyotrophic Sclerosis (ALS) Clinic at Vanderbilt. His research interests include clinical trials in ALS, inflammatory neuropathies, and electrodiagnosis of peripheral neuropathy. Dr. Donofrio has served on the Board of Directors of the American Association of Neuromuscular & Electrodiagnostic Medicine and is a past president of the association. He is board certified by both the American Board of Electrodiagnostic Medicine and the American Board of Psychiatry and Neurology.
How to Evaluate Patients With Suspected Radiculopathy

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INTRODUCTION

Electrodiagnostic (EDX) medicine is a unique area of medicine that differs from other medical and surgical consultations. Electrophysiologic testing is an extension of the history and physical examination and is tailored to the clinical scenario. Like other areas of clinical medicine, high-quality consultations are rendered by physicians with experience and technical competence coupled with an understanding of neuromuscular disorders.

Cervical and lumbosacral radiculopathies are pathological processes affecting the spinal nerve root and suspected radiculopathies are a frequent reason for referrals for EDX testing. This manuscript deals with the clinical approach used in an EDX laboratory to evaluate a person with neck pain, lumbar spine pain, or limb symptoms suggestive of radiculopathy.

SPINE AND NERVE ROOT ANATOMY

The anatomy of the bony spine, supporting ligamentous structures, and neural elements provides a unique biomechanical system that allows both strength as well as flexibility. Because the dorsal root ganglion (DRG) lies in the intervertebral foramen, this anatomical arrangement has implications for EDX testing of radiculopathy. With radicular (intraspinal) lesions, axon damage can result in abnormal spontaneous activity on needle electromyography (EMG) and, possibly, reduced compound muscle action potentials (CMAPs). However, with radiculopathies, the sensory nerve action potentials (SNAPs) are preserved because the site of injury is proximal to the DRG. This anatomical relationship provides a mechanism for further confirming whether or not a lesion is radicular or more peripheral. For most radiculopathies, sensory responses in the limb are preserved. Occasionally, with a far lateral herniation of the disc or with the DRG lying nearer the spinal canal, sensory responses may be reduced in radiculopathy. This is the exception however, and sensory responses are usually preserved in radiculopathy. Loss of sensory nerve responses should prompt the clinician to consider other possibilities, such as plexopathy, mononeuropathy, or polyneuropathy. Needle 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. Imaging of the spine can correlate with EMG findings to determine the site of pathology.

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. Thus EMG failed to accurately identify the compressed root in 16% of patients, however, at least half of discrepancies in this study were attributable to anomalous innervation.

There are many anatomic variations within the cervical nerve roots and the brachial plexus. Perneczky described variations in all 40 cadavers studied to assess deviations from accepted cervical root and brachial plexus anatomy. Lev, Maggiano, and Wilbourn examined the pattern of EMG abnormalities in 50 patients with surgically proven cervical root lesions, with 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 lesions and half demonstrated C7 patterns.
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 and in formulating a differential diagnosis. A focused neuromuscular examination that assesses strength, reflexes, and sensation in the affected limb and the contralateral limb provides a framework for EDX assessment. Other tests for common musculoskeletal disorders, (e.g., shoulder impingement), can provide further insights into the cause of a patient’s symptoms.

The implications of symptoms and signs on EDX findings were investigated by Lauder and colleagues in cohorts of patients with upper or lower limb symptoms and suspected cervical and lumbosacral radiculopathies.5,6 Though physical examination findings better predicted radiculopathy, many patients with normal physical examinations had abnormal EDX studies, indicating that clinicians should not avoid EDX testing simply because the physical examination is normal. For lower limb symptoms, loss of a muscle stretch reflex or presence of weakness dramatically increased the likelihood electromyographic radiculopathy findings. Loss of the Achilles reflex, for instance, resulted in an odds ratio of 8.4 (p<0.01) or 8 times the likelihood of having an S1 radiculopathy on EMG examination.4 Weakness in any leg muscle resulted in about 2.5 times greater chance of identifying a lumbosacral radiculopathy on EMG examination.4

Similar findings were noted for upper limb symptoms. For example, if a reflex was lost or weakness was noted, the likelihood of having an EMG-confirmed cervical radiculopathy was about four times greater than if these exam findings were absent.4 Combinations of findings, particularly weakness plus reflex changes, resulted in a 9-fold greater likelihood of cervical radiculopathy.4

Cannon and colleagues4 studied the ability of physical examination to delineate upper limb musculoskeletal disorders (myofascial pain, shoulder impingement, lateral epicondylitis, de Quervain’s tenosynovitis) and whether these findings predicted the outcomes of EDX testing (normal study, cervical radiculopathy, or another EDX-confirmed diagnosis). They found a total prevalence of musculoskeletal disorders of 42%. Prevalence was greater in those with a normal study (69%) compared with those with cervical radiculopathy (29%, p<0.0001), and 45% in those with another diagnosis (p=0.02). While the prevalence of certain musculoskeletal disorders led to increased likelihood of a normal EDX evaluation, the high prevalence among both patients with normal studies and those with radiculopathy and other disorders limited the usefulness of this information in precisely predicting study outcome. Consequently, the presence of upper limb musculoskeletal disorders should not preclude EDX testing when otherwise indicated.

These same investigators found similar results for lower limb studies.7 In a sample of 170 patients referred for suspected lumbosacral radiculopathy, the total prevalence of musculoskeletal disorders (myofascial pain, trochanteric bursitis, iliotibial band syndrome, or plantar fasciitis) was 32%. The prevalence in those with a normal study was 55%, compared with 21% in those with lumbosacral radiculopathy (p<0.0001). As with suspected cervical radiculopathy, the high prevalence among both patients with normal studies and those with radiculopathy and other disorders limits the usefulness of this information in predicting study outcome. It is common for patients to have two or more problems and the presence of a musculoskeletal disorder should not preclude EDX testing when radiculopathy is suspected.7

GUIDELINES FOR RADICULOPATHY ASSESSMENT

The American Association of Neuromuscular & Electrodiagnostic Medicine’s guidelines recommend that for an optimal evaluation of a patient with suspected radiculopathy, a needle examination (NE) 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.7 NCSs are necessary to exclude polynuropathy. An EDX examination of selected muscles representing all relevant myotomes is the primary means of radiculopathy evaluation. The sufficiency of the EDX examination 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.9 This definition assumes that other generalized conditions such as polynuropathy are not present.

It may be necessary to study the contralateral limb, particularly if the first limb shows EMG findings suggestive of radiculopathy and the patient has symptoms on both sides. If both limbs are abnormal, 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 polynuropathy or motor neuron disease.

For identifying or confirming radiculopathy, H reflexes are generally not very useful. They are used, however, to exclude polynuropathy. Many researchers have evaluated their sensitivity with respect to lumbosacral radiculopathies and have generally found low sensitivities.9,10,17,18,19 They are present bilaterally in 92% of healthy subjects 60-88 years old.10 F waves are late responses involving the motor axons and axon pool at the spinal cord level. As with H reflexes, F waves demonstrate low sensitivities and specificities for radiculopathy; rather, they are a better screen for polynuropathy. Published sensitivities range from 13-69%.9,10,17,18,19 Somatosensory evoked potentials (SEPs) are generally not useful in the evaluation of radiculopathy.9,20,21

ELECTROMYOGRAPHIC DIAGNOSTIC SENSITIVITIES AND SPECIFICITIES

The need for EMG, particularly in relation to imaging of the spine, has been previously highlighted.22 NE is particularly helpful in that false-positive rates for magnetic resonance imaging (MRI) of the lumbar spine are high, with 27% of normal subjects having a disc protrusion.23 For the cervical spine, the false-positive rate for MRI is much lower; 19% of subjects demonstrate an abnormality, but only 10% show a herniated or bulging disc.24
It is important to note that radiculopathies may occur without structural findings on MRI, and likewise, without EMG findings. Because EMG evaluates muscles for the presence of abnormalities (e.g., fibrillations from denervated muscle fibers) indicating motor axon loss, a radiculopathy affecting only the sensory roots or resulting only in demyelination will not result in EMG abnormalities. If the rate of denervation is balanced by reinnervation, then spontaneous activity is less likely to be found.

The sensitivity of EMG for cervical and lumbosacral radiculopathies has been examined in multiple studies. Sensitivity for lumbosacral radiculopathy is unimpressive, ranging from 49-86%. For cervical radiculopathies the sensitivities are similar, from 50-71%.

Tong and colleagues examined the specificity of EDX testing in asymptomatic persons 55 and older. A standardized EDX study was conducted by a blinded EDX physician using a monopolar needle to assess five leg muscles and the paraspinal muscles (PSMs). Included were 30 subjects with a mean age of 65.4 years (standard deviation = 8.0). When only positive sharp waves (PSWs) or fibrillations were used to characterize the subject as having a radiculopathy, (two limb muscles plus associated lumbar PSM abnormal, two limb muscles abnormal, or one limb muscle plus associated lumbar PSM abnormal) 100% specificity was noted. This means there were no false-positive EMG evaluations for radiculopathy. When at least 30% polyphasia in the limb muscles was considered abnormal, the respective specificities were 97%, 90%, and 87%. The specificity for plexopathy was 100% when only PSWs or fibrillations were used, and it remained 100% when increased polyphasias was added. This study demonstrated that NE has excellent specificity for lumbosacral radiculopathy and plexopathy when the appropriate diagnostic criteria are used.

It is apparent that EMG is not a good screening test, while it is helpful to assess the clinical relevance of symptoms and imaging findings. EDX testing is also useful for excluding other disorders such as entrapment neuropathies or polyneuropathy. For example, a patient may have a median neuropathy at the wrist and shoulder impingement, which in combination mimic cervical radiculopathy. The astute EDX physician can clarify the picture with a focused physical examination coupled with EDX testing.

**PARASPINAL MUSCLE EXAMINATION**

Dumitru, Diaz, and King examined the lumbosacral PSMs and intrinsic foot muscles with monopolar NE to assess the prevalence of abnormalities in persons who were asymptomatic. They recorded potentials with similar waveform characteristics such as fibrillations and PSWs. However, by excluding irregularly firing potentials, and including only those potentials that are regularly discharging, they found false-negative paraspinal findings on EMG examination in only 4% of their normal subjects. Previous investigators in less quantitative studies reported higher percentages of false positives. This quantitative study by Dumitru and colleagues underscores the need to assess both firing rate and rhythm, as well as potential morphology when evaluating for fibrillations and positive waves in the lumbar PSMs. EDX physicians should take care not to overcall PSM EMG findings by mistaking irregularly firing endplate spikes for regularly discharging fibrillations.

Additionally, PSMs may be abnormal in patients with spinal cancers, amyotrophic lateral sclerosis, and following spinal surgery or lumbar puncture. Thus, correlation with a clinical history of procedures and symptoms is critical. Investigations by Haig and colleagues have provided insights into better quantification and examination of lumbosacral PSMs, with that examination refined using a grading scale for abnormalities. The mini-PSM score provides a quantitative means of deriving the degree of PSM denervation and more precisely distinguishes normal findings from EMG abnormalities of the lumbar PSMs.

**HOW MANY, AND WHICH, MUSCLES SHOULD BE STUDIED?**

Because electrodiagnosis 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 NE, as indicated from the modest diagnostic sensitivities discussed above. A screening EDX study involves determining whether or not the radiculopathy can be confirmed. If the radiculopathy cannot be confirmed (e.g., only the sensory fibers are affected at the nerve root), then presumably no number of muscles can identify the condition.

The concept of a screening EDX examination encompasses identifying the possibility of an electrodiagnostically confirmable radiculopathy. If one muscle 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 EDX examination, EDX physicians should look for more subtle signs of denervation, and if present in the screening muscles, 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 multicenter study evaluating patients referred to participating EDX laboratories with suspected cervical radiculopathy. A standard set of muscles was 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 encompassed the following: (1) PSWs; (2) fibrillation potentials; (3) complex repetitive discharges; (4) high-amplitude, long-duration motor unit action potentials (MUAPs); (5) increased polyphasic MUAPs; or (6) reduced recruitment. One hundred-one patients with EDX-confirmed cervical radiculopathies representing all cervical root levels were evaluated. When PSMs were one of the screening muscles and neuropathic findings were assessed, five-muscle screens identified 90-98% of radiculopathies, six-muscle screens identified 94-99%, and seven-muscle screens identified 96-100% (Table 1).
The Lumbosacral Radiculopathy Screen

Similarly, a prospective multicenter study was conducted at five institutions by Dillingham and colleagues for patients referred for suspected lumbosacral radiculopathy. A standard set of muscles was examined by NE and findings of 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 PSMs were not part of the screening, four-muscle screens identified 88-97%, five-muscle screens identified 94-98%, and six-muscle screens 98-100% (Table 2). When PSMs were not part of the screen, identification rates were lower for all screens and eight limb muscles were necessary to identify 90%. As with cervical radiculopathy screens, assessing for neuropathic findings increases identification rates. A large retrospective study noted similar findings, concluding that five muscles identified most EDX-confirmable radiculopathies.

Dillingham and Dasher reanalyzed data from a study published by Knutsson almost 40 years earlier. In this detailed study, 206 patients with sciatica underwent lumbar surgical exploration. All subjects underwent a standardized 14-muscle NE using concentric needles. The examiner was blinded to other test results and physical examination findings. In addition to the EMG, standardized data were collected regarding surgical information, myelogram findings, and physical examination findings. In this reanalysis, screens of four muscles, one being the lumbosacral paraspinal muscles, led to marginal increases in identification. Individual screens useful to the EDX physician are listed in Table 1. In some instances, a particular muscle cannot be studied due to wounds, skin grafts, dressings, or infections. The physician can use an alternative screen with equally high yield. These findings were consistent with those derived from a large retrospective study.

### Table 1. Six-muscle screen identifications of patients with cervical radiculopathies

<table>
<thead>
<tr>
<th>Muscle screen</th>
<th>Neurpathic (%)</th>
<th>Spontaneous activity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Six muscles without paraspinals:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deltoid, APB, FCU, triceps, PT, FCR</td>
<td>93</td>
<td>66</td>
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<td>Biceps, triceps, EDC, PT, APB, FCU</td>
<td>94</td>
<td>64</td>
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<tr>
<td>Deltoid, triceps, PT, APB, EDC, PSM</td>
<td>99</td>
<td>83</td>
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APB = abductor pollicis brevis; FCU = flexor carpi ulnaris; PT = pronator teres; FCR = flexor carpi radialis; FDI = first dorsal interosseous; EDC = extensor digitorum communis; PSM = cervical paraspinal muscles


When PSMs were not part of the screen, the identification rates were consistently lower. The study of eight distal limb muscles recognized 92-95% of radiculopathies. If one only considers fibrillations and PSWs in the EMG assessment, identification rates are lower. Six-muscle screens including PSMs yielded consistently high identification rates and studying additional muscles led to marginal increases in identification. Individual screens useful to the EDX physician are listed in Table 1. In some instances, a particular muscle cannot be studied due to wounds, skin grafts, dressings, or infections. The physician can use an alternative screen with equally high yield. These findings were consistent with those derived from a large retrospective study.

### Table 2. Six-muscle screen identifications of patients with lumbosacral radiculopathies

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<td></td>
</tr>
<tr>
<td>ATIB, PTIB, MGAS, RFEM, SHBF, LGAS</td>
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<td>78</td>
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<tr>
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ATIB = tibialis anterior; PTIB = tibialis posterior; MGAS = medial gastrocnemius; LGAS = lateral gastrocnemius; TFL = tensor fascia lata; SHBF = short head of biceps femoris; ADD = adductor longus; VLAT = vastus lateralis; VMED = vastus medialis; RFEM = rectus femoris; PSM = lumbar paraspinal muscles


Knutsson almost 40 years earlier. In this detailed study, 206 patients with sciatica underwent lumbar surgical exploration. All subjects underwent a standardized 14-muscle NE using concentric needles. The examiner was blinded to other test results and physical examination findings. In addition to the EMG, standardized data were collected regarding surgical information, myelogram findings, and physical examination findings. In this reanalysis, screens of four muscles, one being the lumbosacral PSMs, 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.

This study, using data from 4...
decades ago, confirmed that a four-muscle screen provides high identification. These findings are consistent with contemporary work showing that screens with relatively few muscles (six) are sufficient.

As described above, recent research efforts were undertaken to refine and streamline the EDX examination. The strongest studies, contemporary prospective multicenter investigations, provide the best estimates of a sufficient number of muscles. In summary, for both cervical and lumbosacral radiculopathy screens, the optimal number of muscles appears to be six, including the PSMs and representing all root levels. When paraspinal muscles are not included, then eight nonparaspinal muscles must be examined.

Another way to think of this is, “to minimize harm, six in the leg and six in the arm.”

If one of the six muscles studied in the screen demonstrates neuropathic abnormalities, the examiner must study additional muscles. NCCs should also be done to determine if this muscle finding is due to a mononeuropathy. If more extensive EDX testing reveals that the findings are limited to a single muscle, and NCCs exclude mononeuropathy, then the single muscle finding remains of uncertain clinical relevance, particularly if the findings were subtle (e.g., reduced recruitment).

If none of the six muscles is abnormal, the examiner can be confident that by EDX testing there is no radiculopathy and can discontinue testing. The patient may still have a radiculopathy. Other tests such as MRI should be used for further assessment for radiculopathy. This logic is illustrated in Figure 1.

Figure 1 Decision algorithm for radiculopathy assessment with needle EMG

![Figure 1 Decision algorithm for radiculopathy assessment with needle EMG](image)

It is important to remember that EDX testing for cervical and lumbosacral radiculopathies were validated in a group of patients with limb symptoms suggestive of radiculopathies. These tests 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 and expanding the examination as data are acquired.

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 abnormal EMG findings did not demonstrate PSM abnormalities, only limb muscle findings. For 76% of patients, the EMG showed bilateral myotomal involvement.

When reporting EDX conclusions regarding the presence or absence of a radiculopathy, the EDX physician utilizes the pattern of muscle involvement to identify the minimum number of root levels to explain these EMG findings. Most muscles have at least dual root innervations and this fact, coupled with anatomic variations, does pose challenges. For lumbosacral radiculopathies in which the gastrocnemius muscles and PSMs are involved, and the quadriceps, tibialis anterior, and gluteus maximus are spared, for instance, this points to a single level (S1) and more discrimination by the EDX physician is possible. It is important to remember, however, that such information must be correlated with imaging because the S1 root can be involved anywhere along its course through the cauda equina and intervertebral foramina.

In the cervical region it is often difficult to sort out precisely the level of involvement, as many commonly studied muscles have shared innervations (e.g., deltoid, biceps, infraspinatus, supraspinatus all with C5 and C6 innervations). A sufficient number of muscles must be studied to examine the pattern of involvement and report the minimum number of roots needed to explain the findings. Sometimes this is one root and other times two roots are equally likely to explain all of the findings. The EDX physician should not convey more precision than the muscle patterns of involvement support. A sufficient number of muscles should be studied to discern such patterns. The six-muscle screen is only a screening tool. If a muscle is positive, the implications of this abnormality must be explored by examining other muscles in that peripheral nerve distribution, other similarly innervated muscles, and more muscles innervated by roots above and below the root that innervates the muscle with EMG findings.

Another issue with drawing EDX conclusions is the strength of various EMG evidence of denervation (motor axonal loss). A pattern of unequivocal fibrillations in a myotomal distribution is quite compelling for radiculopathy. Other softer findings such as reduced recruitment, for instance, should inspire less confidence in the diagnostic conclusions. More subjective findings (reduced recruitment) are open to interpretation and best appreciated by skilled EDX physicians and care should be taken not to overcall radiculopathy. Polyphasic potentials must be easily recognized, involve a large proportion (>30%) of recruited motor units, and demonstrate long durations. If quite marked and in a myotomal distribution they may indicate radiculopathy but this is a less strong call for EDX physicians. In such cases the contralateral limb should be examined to insure there is not a generalized process occurring.
References

BASICS WITH THE EXPERTS


Median and Ulnar Entrapment Neuropathies

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INTRODUCTION

Median and ulnar neuropathies are the most common neuropathies of the upper limbs and are most commonly caused by entrapment. Though common, they also remain commonly debated and reviewed in terms of the most effective electrophysiologic evaluation which complements the clinical presentation and course. As in approaching any electrodiagnostic (EDX) study, the key question to be answered for the clinical scenario is most pertinent. Is the physician trying to rule in a suspected clinical diagnosis, rule out alternative diagnoses, and/or trying to localize a lesion and determine its severity, and ultimately, prognosis? Electrophysiologic information may be critical to guide treatment endeavors.

IDENTIFICATION OF ENTRAPMENT NEUROPATHIES

The basic principles of nerve conduction studies (NCSs) and needle examination (NE) apply in the identification of entrapment neuropathies. The anatomical course of the peripheral nerve is of critical importance, including potential sites of compression for typical or unusual anatomic structures. Injury from trauma, fracture, and other wounds is noteworthy but is not included in the scope of this discussion. Peripheral nerves do not always follow a typical course, and at times fibers from one nerve may travel with another, known as anomalous innervation, which may confound studies. Within each nerve, the nerve fascicles may be bundled together in such a way as to create the appearance of a nerve lesion at one level, when indeed it occurs at another. Avoiding the typical technical pitfalls of performing NCSs and NE holds true. Finally, the challenge of selecting the highest yield tests for the question to be answered is key to designing a test strategy that is the least uncomfortable for the patient, the least costly, and the least time consuming for the physician and patient. Assessment of both the sensory and motor fibers of the peripheral nerve should be included in the study. Excessive testing is to be avoided (Table 1).

Median Nerve Entrapment

The most common entrapment of the median nerve is at the wrist and typically causes a syndrome we know as carpal tunnel syndrome (CTS). Other areas of potential entrapment are relatively rare (Table 2). With median nerve symptoms, entrapment at any level, from the origin of the nerve to the digital nerves must be considered in an initial differential diagnosis. This includes radiculopathy, brachial plexopathy, and more proximal median nerve injury. Because CTS is so common, and slowing of median nerve conduction at the wrist can exist in some patients without clinically significant CTS, often assuring that median nerve symptoms result from carpal tunnel compression alone can be difficult.

Table 1. Essentials of entrapment neuropathies

<table>
<thead>
<tr>
<th>Essentials of entrapment neuropathies</th>
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<tbody>
<tr>
<td>• Understand the peripheral nerve anatomy including the typical course of the nerve, potential anomalous innervation, and organization of nerve fascicles.</td>
</tr>
<tr>
<td>• Identification of conduction block and impact of volume conduction and temperature.</td>
</tr>
<tr>
<td>• Design an efficient and cost effective study of the sensory and motor fibers.</td>
</tr>
<tr>
<td>• Not all isolated peripheral nerve injury results from entrapment.</td>
</tr>
</tbody>
</table>
MEDIAN AND ULNAR ENTRAPMENT NEUROPATHIES

Volkman’s ischemic contracture (compartment syndrome) and specificity values represent the lower andrist in the nerve conduction between wrist and Direct trauma to define an abnormal value, and differences in the average severity of the CTS patients in the present (Table 3).

The EDX findings do not confirm that compression should not be used in isolation to confirm or rule out a diagnosis. On examination, weakness or atrophy of the thenar muscles can function such as gripping tasks, opening jars, and holding items. CTS resulting from median neuropathy at the wrist is the most affected, possibly because of focal compression of the recurrent branch of the median nerve or selective effects on fascicles within the median nerve at the wrist.

There are many approaches for evaluating median sensory conductions across the wrist, and it is critical to think through these alternative approaches even before seeing the patient. As mentioned above, the EDX physician or technician should not adopt the methodology of performing one test and, upon finding a normal result, performing another test until an abnormality is found. Although this might seem intuitively tempting, it is risky since each additional test performed carries about a 2.5% false-positive rate, which is roughly additive as each new test is performed. For example, performing three separate tests, and making a diagnosis upon any one abnormality carries about a 7.3% false-positive rate.

When selecting sensory NCSs, studies should be selected that are (in descending order of importance): (1) specific (few false positives), (2) sensitive (few false negatives), (3) reliable (obtain the same results today and tomorrow), and, (4) little influenced by covariates such as temperature and age (Table 4).

Patients presenting with CTS may or may not have these symptoms related to compression and other etiologies must be considered. The EDX findings do not confirm that compression is the mechanism, only that a median neuropathy at the wrist is present (Table 3).

### Table 2. Median nerve entrapment sites

| Carpal tunnel |
| Forearm entrapment: |
| • Volkman’s ischemic contracture (compartment syndrome) |
| • Hemorrhage – needle injury, arteriovenous fistula |
| Anterior interosseous nerve (Kiloh-Nevin syndrome): |
| • Direct trauma |
| • Gantzer’s muscle – accessory flexor pollicis longus or anomalous fibrous bands |
| Pronator syndrome: |
| • Pronator teres |
| • Bicipital aponeurosis (lacertus fibrosus) – antebrachial fascia thickening |
| • Struthers’ ligament (supracondylar spur) – 3-6 cm proximal to medial epicondyle of humerus |

More proximal lesions are more typically due to trauma of the arm rather than entrapment.

### Median Neuropathy at the Wrist

CTS resulting from median neuropathy at the wrist is the most common entrapment neuropathy referred to EDX laboratories in the United States. Typically the patient is referred for hand pain, numbness, tingling, and weakness or difficulty with function such as gripping tasks, opening jars, and holding items. Often the perceived numbness includes the entire hand. The most typical symptoms of CTS include hand numbness and weakness. Symptoms are usually worse at night and patients may occasionally report they flick their wrist to relieve symptoms. On examination, weakness or atrophy of the thenar muscles can be found and possibly some mildly reduced sensation. There are a number of physical signs such as Tinel’s sign, Phalen’s sign, and the flick sign which can be suggestive of CTS. However, the sensitivity and specificity of these tests are not high and they should not be used in isolation to confirm or rule out a diagnosis.

### Table 3. Median neuropathy mnemonic

\[
P = \text{Pregnancy} \\
R = \text{Rheumatoid arthritis} \\
A = \text{Amyloidosis} \\
G = \text{Graves’ disease (thyroid disorders), gout} \\
M = \text{Myeloma, mass, other space occupying lesions} \\
A = \text{Abnormal anatomy, acromegaly} \\
T = \text{Tensynovitis} \\
I = \text{Infection, inflammation} \\
C = \text{Compression}
\]

### Table 4. Comparison of pooled sensitivities and specificities of EDX techniques to diagnose CTS

<table>
<thead>
<tr>
<th>Technique</th>
<th>Pooled sensitivity</th>
<th>Pooled specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Median sensory and mixed nerve conduction: wrist and palm segment compared to forearm or digit segment</td>
<td>0.96</td>
</tr>
<tr>
<td>B</td>
<td>Comparison of median and ulnar sensory conduction between wrist and ring/finger</td>
<td>0.97</td>
</tr>
<tr>
<td>C</td>
<td>Median sensory and mixed nerve conduction between wrist and palm</td>
<td>0.97</td>
</tr>
<tr>
<td>D</td>
<td>Comparison of median and ulnar mixed nerve conduction between wrist and palm</td>
<td>0.61</td>
</tr>
<tr>
<td>E</td>
<td>Median motor nerve conduction between wrist and palm</td>
<td>0.61</td>
</tr>
<tr>
<td>F</td>
<td>Comparison of median and radial sensory conduction between wrist and thumb</td>
<td>0.61</td>
</tr>
<tr>
<td>G</td>
<td>Median sensory nerve conduction between wrist and digit</td>
<td>0.54</td>
</tr>
<tr>
<td>H</td>
<td>Median motor nerve distal latency</td>
<td>0.97</td>
</tr>
<tr>
<td>I</td>
<td>Median motor nerve terminal latency index</td>
<td>0.87</td>
</tr>
<tr>
<td>J</td>
<td>Comparison of median motor nerve distal latency (second tendon) to the ulnar motor nerve distal latency (second intersite)</td>
<td>0.87</td>
</tr>
<tr>
<td>K</td>
<td>Sympathetic skin responses</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Detection of the slowing of median nerve conduction across the wrist is the most useful way to confirm the diagnosis. Many approaches are described for diagnosing CTS using NCSs. For a more in-depth review, readers are encouraged to review other articles. The general approach should be to measure sensory and motor conduction across the wrist and to compare the latencies with nearby nerves in the hand such as the radial or ulnar nerve, which do not traverse the carpal tunnel. This comparison helps to exclude the effects of temperature, age, and other general factors including occupation, which may influence nerve conduction. As is the case in most entrapment neuropathies, sensory fibers are usually affected first. Rarely, motor axons are preferentially affected, possibly because of focal compression of the recurrent branch of the median nerve or selective effects on fascicles within the median nerve at the wrist.
The approach at Mayo Clinic typically begins with median and ulnar motor conduction studies first. If this demonstrates slowing or low amplitude of the median nerve, either absolutely or relative to the ulnar study, then typically the median antidromic sensory to the index finger and ulnar antidromic sensory to the small finger studies are performed. The reasoning is that a sensitive study is no longer needed to detect a median neuropathy at the wrist, and the antidromic studies typically yield more reliable amplitudes and conduction velocities than the other tests for median neuropathy at the wrist. However, if the motor conduction studies are completely normal, then a sensitive test is not needed for relative median nerve slowing at the wrist. Typically, the author then performs the median and ulnar palmar orthodromic studies. If these are also normal, depending on the clinical scenario and purpose of the study, then a NE would be performed to exclude other diagnoses. If none are found, and depending on the clinical question being asked, further NCSs, including median-ulnar antidromic sensory to the ring finger, median-radial antidromic sensory to the thumb, or, atypically, mid-palmar conduction to the middle finger may be considered. If the median motor study shows potential conduction block more proximally, ultrasound evaluation of the nerve with guidance to test for focal conduction block along the nerve may be performed with NE assistance to help define a more proximal nerve lesion.

Dr. Lawrence Robinson has also published extensively on a method to summarize these three tests into one result known as the combined sensory index (CSI). To calculate the CSI, all three of the studies mentioned above are performed and he adds the latency differences (median minus ulnar or median minus radial) together. When these are negative, (i.e., the median is faster), a negative number is used. The CSI, because it summarizes three different tests, has been shown to be highly specific and more sensitive than the individual tests.11 It is also more reliable than single tests when the same patient is studied on two different occasions.11 A CSI exceeding 0.9 ms is considered abnormal.12 However, in most cases, performing all three tests will not be necessary, and for this reason the CSI is not used often in many laboratories. Motor NCSs are also, as mentioned above, an essential component of the EDX evaluation of CTS. These should be performed even if sensory conduction studies are normal, since in rare cases there may be greater motor fiber involvement than sensory fiber involvement, resulting either from differential nerve fascicle involvement or a nonentrapment etiology. Most commonly, studies are performed with stimulation of the median nerve at the wrist and recording over the abductor pollicis brevis (APB). Generally, latencies exceeding 4.5 ms are considered abnormal. It is often not useful to compare one median nerve with the other side because of the frequency of bilateral CTS. However, some EDX physicians compare the median motor latency with the ulnar motor latency; a difference exceeding 1.5 ms is considered abnormal. While some authors do advocate stimulating both at the wrist and at the palm,14 it is difficult to stimulate only the median nerve in the palm, and a false diagnosis is possible if the ulnar nerve is stimulated in the palm.15

NE is sometimes useful in evaluating patients with CTS.16 There is not a consensus about when thenar muscle electromyography (EMG) should be performed. However, once again, the physician is not typically trying to prove that the patient has CTS only, but is trying to exclude other concerns in the differential diagnosis. Hence, NE of the limb should be included. NE of the APB or opponens pollicis is important to assess for subtle motor nerve fiber involvement in patients with normal motor conduction studies, thereby better defining severity, potential treatment interventions, and outcome.

The study interpretation should state that the patient has a median neuropathy at the wrist. This does not necessarily mean they have CTS per se, as the syndrome itself is a clinical one. Median neuropathy at the wrist is the electrophysiologic equivalent. Median neuropathy at the wrist can be judged to be mild, moderate, or severe. CTS, however, can only be judged clinically in terms of severity, and the EDX findings serve as an adjunct to the clinical treatment decisions. It is preferable to include the following components: diagnosis, localization, pathophysiology (axon loss and/or demyelination), and chances for successful treatment (if known).17 There has been some work18,19 which allows EDX physicians to give the referring physician an indication of the likelihood of successful outcome from carpal tunnel release. When NCSs are normal, carpal tunnel release may only result in resolution of symptoms about 40% of the time. When median sensory and motor responses are absent, carpal tunnel release may result in symptom resolution about 23% of the time, and 45% of the time when the sensory response is absent and motor latency is prolonged greater than 6.5 ms. If there are only mild sensory findings, about 50-60% of individuals will have relief of symptoms after carpal tunnel release.

Evaluation of patients with CTS after release requires special consideration. Although patients with CTS usually have some improvement in latency after successful surgical treatment, latencies do not always return to the normal range. The structure of the myelin covering, after demyelination and remyelination, is not the same as it was before entrapment and some slowing often persists. Thus, when examining a patient with symptoms after surgery, it is important to either compare with pre-operative studies or evaluate at two points in time after treatment to look for either improvement or worsening. Prolonged latencies by themselves do not indicate the need for reoperation.

**Ulnar Nerve Entrapment**

The ulnar nerve has many potential sites of entrapment and a number of individual syndromes resulting from lesions at various sites, many due to direct nerve pressure, irritation, or trauma rather than entrapment alone (Table 5). As with CTS, the EDX approach will depend on the question being asked and the clinical history and examination. A key difference in approach to the ulnar nerve evaluation is the opportunity to fairly reliably perform both short segment stimulation to determine conduction block in the region of the elbow, as well as axillary and supraclavicular stimulation to evaluate the nerve more proximally.
Ulnar Neuropathy at the Elbow

Ulnar neuropathy at the elbow (UNE) is another common entrapment neuropathy, second only to CTS presenting to the EDX physician. The etiology of UNE varies but can be due to acute injury, entrapment in the cubital tunnel, or prolonged stretching of the nerve in the ulnar groove when the elbow is held in the flexed or flexed and pronated position. Tardy ulnar palsy is a result of prior elbow injury causing an elbow deformity and slowly progressive injury to the ulnar nerve. Symptoms of ulnar neuropathy typically include numbness over the small finger and the ulnar half of the ring finger. Generally, UNE also affects sensation over the dorsum of the hand on the ulnar side, an area supplied by the dorsal ulnar cutaneous nerve, which branches from the ulnar nerve proximal to the wrist, most typically at the junction of the distal third and proximal two thirds of the forearm. By contrast, ulnar nerve lesions at the wrist spare the dorsal ulnar cutaneous territory because they are distal to this branch point. UNE should spare sensation over the medial forearm, as the medial forearm is supplied by the medial antebrachial cutaneous nerve coming off the medial cord of the brachial plexus. A key point of clinical differentiation is that medial forearm sensory symptoms may arise from a plexopathy, a low cervical or T1 radiculopathy, and not ulnar neuropathy.

Patients often also present with weakness of ulnar hand muscles and complain that they have difficulty holding things and difficulty with grip strength. They may sometimes notice atrophy of the first dorsal interosseous (FDI) muscle. At times, they will report that when they put their hand into their pocket, the small finger does not make it in. This is known as Wartenberg’s sign and reflects weakness of the interosseous muscles, specifically the adductor of the small finger.

On physical examination, the physician will often note weakness of interosseous muscles, atrophy of the FDI, and reduced sensation in the ulnar nerve territory in the hand. There may also be a Froment’s sign, indicating weakness of the adductor pollicis and the FDI. A Tinel’s sign can often be noted at the elbow, but this is nonspecific and can be seen in a number of normal, healthy individuals.

Because sensory conduction is difficult to reliably record across the elbow, most EDX physicians will rely upon motor conduction studies of the ulnar nerve. There are a number of technical elements to keep in mind when performing these studies. First, it is advisable to record from both the abductor digiti minimi (ADM) and the FDI at the same time, utilizing two channels of the EMG instrument. Although each muscle has similar sensitivity for detecting UNE, there is not a complete overlap and sometimes one muscle will demonstrate conduction block when the other one does not. Stimulation usually is performed at the wrist, below the elbow and above the elbow. When stimulating across the elbow, the elbow should be in a bent position with a roughly 70°-90° angle. This is important because it stretches the nerve through the ulnar groove. If the elbow is not bent, it is still long enough to accommodate elbow flexion but is redundant upon itself. Therefore, surface measurement across the skin will underestimate the true nerve distance and the calculated conduction velocity will be erroneously slow.

There has been discussion in the literature about minimum distances to use between the above and below elbow stimulation sites. Earlier literature suggested that, in general, there should be at least 10 cm of distance between stimulation sites. However, this was based upon measurements of error in the 1970s, when measuring latencies on equipment using much older technology. Similar studies have now been repeated utilizing modern digital equipment, and this has demonstrated that a 6 cm distance should usually be sufficient, and would have errors similar to the 10 cm distance from the predigital era 30 years ago.

When performing ulnar motor conduction studies, there should be an awareness of the potential impact of Martin-Gruber anastomosis. This anastomosis is present in 15-20% of individuals, and typically involves fibers crossing from the median nerve to the ulnar nerve in the proximal forearm. At times, the fibers can originate from the anterior interosseous nerve rather than from the main branch of the median nerve. In the presence of Martin-Gruber anastomosis, recordings will show a normal large amplitude response from the ADM and FDI when stimulating the ulnar nerve at the wrist. However, while stimulating the ulnar nerve at the elbow, there will be a decreased amplitude response because only the ulnar nerve fibers are stimulated and not those that cross in the proximal forearm. To the inexperienced EDX physician or technician, this can masquerade as conduction block in the proximal forearm and can result in an erroneous diagnosis. The indication of a Martin-Gruber anastomosis, rather than ulnar neuropathy in the forearm or elbow, is that this drop in amplitude occurs between wrist and below elbow and not across the elbow. The presence of this anomalous innervation can be proven by stimulating the median nerve at the elbow and recording from the ADM and FDI muscles. When a crossover exists, a sizable response can be recorded from these usually ulnar-innervated muscles.

<table>
<thead>
<tr>
<th>Ulnar nerve entrapment sites</th>
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</thead>
<tbody>
<tr>
<td>Arcade of Struthers-fascia from the upper surface of the triceps to the intramuscular septum to the medial triceps</td>
</tr>
<tr>
<td>Struthers’ ligament (rare)</td>
</tr>
<tr>
<td>Ulnar neuropathy at the elbow (most common)</td>
</tr>
<tr>
<td><strong>Intracondylar ulnar nerve pressure</strong> – single or repetitive, chronic subluxation, pressure from bony deformity, masses, and rarely from anconeus epitrochlearis muscle</td>
</tr>
<tr>
<td><strong>Cubital tunnel syndrome</strong> – proximal edge of flexor carpi ulnaris aponeurosis or arcuate ligament</td>
</tr>
<tr>
<td><strong>Tardy ulnar palsy</strong> – late sequelae of bony injury and hence deformity</td>
</tr>
<tr>
<td><strong>Dorsal ulnar cutaneous neuropathy</strong> – typically not entrapped</td>
</tr>
<tr>
<td><strong>Ulnar neuropathy at the wrist</strong> – Guyon’s canal (second most common)</td>
</tr>
<tr>
<td>• Proximal or in Guyon’s canal</td>
</tr>
<tr>
<td>• In Guyon’s canal, hook of hamate at origin - ADQ and FDQ, or in ODQ muscle, or distal to hypothenar muscle branch</td>
</tr>
<tr>
<td>• In Guyon’s canal at hook of hamate in palmaris brevis</td>
</tr>
<tr>
<td><strong>Ulnar neuropathy in the hand-direct pressure</strong></td>
</tr>
</tbody>
</table>

ADQ = abductor digiti quinti, FDQ = flexor digiti quinti, ODQ = opponens digiti quinti
After recording ulnar conduction motor studies across the elbow, a decision should be made about whether these velocities are normal or not. There have generally been two ways to do this. Many authors advocate comparing ulnar conduction across the elbow to that recorded in the forearm. However, this comparison is flawed in that it assumes that ulnar conduction in the forearm is unaffected by a neuropathy proximally at the elbow. Unfortunately, this is not the case since with motor axon loss there is distal slowing due to preferential loss of the faster conducting fibers. As a result, comparison between the two segments is not valid. The other method for determining whether the conduction is normal is to compare the velocity to reference values. This has been shown to be preferable in terms of sensitivity and specificity.

When there is concern for UNE, it is frequently useful to perform ulnar inching studies. These studies involve stimulation of the ulnar nerve at 2 cm increments across the elbow, looking for any focal slowing or conduction block. Latency differences exceeding 0.7 ms or amplitude differences exceeding 10% are suggestive of a focal lesion. It is preferable to see both latency and amplitude changes, as well as changes in morphology, to be certain of a focal lesion. Because the distances are small, and the error in measurement is large as a percentage, the conduction velocity of inching studies should not be considered in ms, but rather look at the established reference values (<0.7 ms) for latency differences across 2 cm.

Ulnar sensory conduction studies can be useful at times. In UNE, when stimulating at the wrist and recording at the small finger, responses are usually small in amplitude or absent. The response from the dorsal ulnar cutaneous nerve can be useful to distinguish ulnar neuropathy at the wrist versus at the elbow. In UNE, it should be affected to a similar degree as the ulnar sensory response to the small finger, but it should be spared in ulnar neuropathy at the wrist.

Because UNE can often have a predominance of axon loss over demyelination, NE should generally be performed in patients referred for UNE, including the ADM, DFI, flexor digitorum profundus, and flexor carpi ulnaris (FCU). Remember, however, that the FCU are often spared in UNE. The intraneural fibers to the FCU are more medial than those to more distal ulnar muscles and hence relatively immune to compression in the area of the groove. In some cases, the flexor digitorum profundus (ulnar portion) may also be spared. When there are abnormalities in the ulnar innervated hand muscles, it is important to check non-ulnar innervated C8/T1 muscles to look for root or plexus lesions that might mimic an ulnar neuropathy. Generally, it is useful to check flexor pollicis longus and extensor indicis proprius in these situations. Checking the APB may be confounded by a co-existing median neuropathy at the wrist or by erroneously inserting the needle into the deep ulnar innervated thenar muscles.

With respect to prognosis, recent studies have suggested that the presence of conduction block is associated with a relatively favorable outcome, and a reduced compound muscle action potential (CMAP) amplitude suggests a poorer prognosis. Nevertheless, a substantial proportion of patients without any CMAPs in hand muscles initially will still have substantial recovery in function.

**SUMMARY**

The EDX physician plays an important role in the diagnosis and localization of median and ulnar nerve lesions. Many different sites of injury are possible along the course of the median and ulnar nerves. Careful selection of the most optimum set of tests to ease patient comfort, time, and cost, with the highest yield in terms of diagnosis, localization, determination of severity, and prognosis requires physician expertise, as this is an iterative process. The EDX findings must always take into account the clinical history and physical examination, and be interpreted within the context of the clinical significance of the problem. The extent of testing will vary between individuals depending on the referring provider’s question, differential diagnosis, the patient’s situation in terms of quality of life, occupation or vocation, and discomfort, and other issues such as in the case of iatrogenic injury or medical legal proceedings. It is critical to attend to the details of clinical evaluation, testing, and interpretation which cannot be approached in a cookbook fashion since each scenario is unique.

**Acknowledgement**

I wish to acknowledge my colleague, Dr. Lawrence Robinson, University of Washington, for his input in developing this handout, which is revised from our previous joint presentations at American Association of Neuromuscular and Electrodiagnostic Medicine courses.
REFERENCES

Weakness is a protean complaint. When pressed for a more precise description, patients initially complaining of generalized weakness may describe fatigue with exertion, as with anemia, reduced cardiac output, or systemic illness. They may also describe hypersomnolence, amotivation, or even an epileptic aura. When referring to motion across a specific joint, weakness may be used to describe pain-limited movement related to musculoskeletal or orthopedic injury.

Patients with true neuromuscular weakness generally present to the physician with loss of function or negative symptoms, such as inability to stand from low-seated positions, inability to climb or descend stairs, unsteady gait with falls, inability to button clothing or manipulate small objects, difficulty chewing tough meats or candies, difficulty speaking clearly or swallowing, or inability to keep eyelids open. A focused clinical history should assess whether a patient has neuromuscular weakness, document what loss of function has occurred, and suggest the distribution of muscles involved.

Neuromuscular weakness may be associated with pain, and the location and quality of the pain may help to determine if the issue is orthopedic, musculoskeletal, peripheral neuropathic, or possibly myopathic. Muscle cramping is generally associated with motor neuropathic processes, and very rarely may suggest a metabolic muscle disorder, especially a glycogenolytic disorder such as myophosphorylase or phosphofructokinase deficiency.

Electrodiagnostic (EDX) studies test clinical hypotheses regarding neuroanatomy that are suggested by the symptoms and clinical findings, and the EDX assessment always begins with a focused clinical history and examination. When assessing neuromuscular weakness, the anatomy of interest is the motor unit. The motor unit is comprised of the anterior horn cell or motor neuron and its terminal ramifications, neuromuscular junctions, and associated muscle fibers.

Focal weakness within one limb or body region associated with local sensory abnormalities suggests a mononeuropathy, plexopathy, or radiculopathy. Multifocal or more generalized weakness associated with abnormal sensation may suggest polyneuropathy or polyradiculopathy, while generalized weakness without abnormal sensation suggests a motor neuron disorder, neuromuscular junction disease, or myopathy.

ELECTRODIAGNOSTIC TECHNIQUES IN NEUROMUSCULAR WEAKNESS

Sensory Nerve Conduction Studies

In sensory nerve conduction studies (NCSs), a sensory or mixed nerve is stimulated either proximally (antidromic technique) or distally (orthodromic technique). The resulting sensory nerve action potential (SNAP) is recorded using surface recording and reference electrodes placed at a prescribed distance apart over the corresponding mixed or sensory nerve. The amplitude of the SNAP reflects the number of functional sensory nerve fibers in a sensory or mixed nerve. The SNAP amplitude may be reduced in nerve disease distal to the dorsal root ganglion, (e.g., plexopathy or neuropathy). While weakness may occur exclusive of sensory neuropathy, the presence of sensory neuropathic findings helps to define the scope of peripheral nerve pathology in neuromuscular disease resulting in weakness.
Motor Nerve Conduction Studies

In motor NCSs, a motor or mixed nerve is stimulated to elicit a compound muscle action potential (CMAP). The CMAP is a summated response from all of the individual muscle fiber action potentials elicited by motor nerve stimulation. The CMAP waveform amplitude reflects the number of functional motor axons within a nerve, as well as the number of functional neuromuscular junctions and muscle fibers within a muscle. CMAP duration and configuration reflect the synchrony of the corresponding, summated muscle fiber action potentials. CMAP latency measurements reflect the myelination status of the nerve.

The CMAP is recorded with three surface electrodes: a recording electrode placed over the motor point or endplate region of the muscle, a reference electrode generally placed over the distal tendon of the muscle, and a ground electrode placed in the same limb away from the active muscle. CMAP parameters include amplitude (measured from baseline to negative peak) and latency (measured to onset). When two points of the nerve are stimulated over a measured distance, a motor nerve conduction velocity can be calculated from the CMAP latencies elicited by distal and proximal stimulation. The CMAP generated with proximal stimulation should have an amplitude no more than 25% lower than that generated with distal stimulation.

The F wave is a late CMAP resulting from proximal propagation of motor nerve impulses to the anterior horn of the spinal cord with backfiring of individual anterior horn cells, resulting in a surface recorded motor unit action potential. F wave latency reflects the functional status of proximal portions of the nerve, such as the plexus and nerve root.

Low CMAP amplitude may result from a reduction in the number of functional motor axons in focal disease (mononeuropathy, plexopathy, or radiculopathy), as well as from widespread disease of motor nerves or neurons (e.g., Guillain-Barré syndrome [GBS], amyotrophic lateral sclerosis, or spinal muscular atrophy). A decrease in the number of functional muscle fibers in myopathy or in neuromuscular junction disease (e.g., Lambert-Eaton myasthenic syndrome) may also reduce CMAP amplitude. Anomalous innervation, such as a Martin-Gruber anastomosis, may result in a low amplitude median CMAP with wrist stimulation. Finally, technical factors such as electrode misplacement and submaximal stimulation can elicit apparently low CMAP amplitude.

Prolonged CMAP latencies and reduced conduction velocities are observed with nerve demyelination. With acquired nerve disease, demyelination is typically observed in a segmental distribution: focal with compression and multifocal with immune mediated nerve diseases such as GBS, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy. In hereditary neuropathies involving demyelination such as Charcot-Marie-Tooth disease type 1A and metachromatic leukodystrophy, the myelin pathology is uniformly distributed along all nerves.

Segmental demyelination may be manifest by motor conduction blocks and temporal dispersion of the CMAP. In one definition of conduction block, CMAP amplitude is reduced by at least 50% with proximal compared to distal nerve stimulation, due to a failure of motor nerve fibers to propagate nerve impulses. With temporal dispersion, the motor nerve impulses within a nerve are differentially slowed across a focally diseased nerve segment. The nerve impulses become desynchronized, and phase cancellation of the resulting muscle fiber action potentials results in a low amplitude and prolonged CMAP. As a practical matter, conduction block is almost always associated with some degree of temporal dispersion.

Repetitive Nerve Stimulation Testing

Repetitive nerve stimulation (RNS) testing may confirm a suspected neuromuscular transmission disorder. The basis for RNS testing relates to the interaction between depletion of immediately-releasable acetylcholine (ACh) stores and presynaptic calcium concentration with manipulation of nerve stimulation rates. The rates have different influences on the safety factor, which represents the extra amount of ACh released at the neuromuscular junction beyond the minimum necessary for the muscle fiber endplate to reach threshold. Slow firing rates (less than 5 Hz) reduce the safety factor in all circumstances and may elicit CMAP decrement in any disease of neuromuscular transmission. High firing rates (10 Hz or greater) or brief exercise (10 seconds of maximum voluntary isometric muscle contraction of the tested muscle or maximum voluntary contraction [MVC]) cause a net increase in presynaptic calcium concentration, improve the safety factor in disorders of ACh release, and may elicit CMAP amplitude and area facilitation.

RNS testing is performed with the same recording scheme that is used for motor NCSs. Trains of stimuli are delivered at an intensity of 10-25% above the level needed to activate all muscle fibers of a motor or mixed nerve. With appropriate technique in low frequency RNS in myasthenia gratis the fourth or fifth CMAP amplitude will be the lowest due to depletion of immediate ACh stores. With mobilization of secondary ACh stores, CMAP amplitudes typically increase slightly after the fourth stimulation, resulting in a saddle- or U-shaped series of CMAP waveforms. Decrement is typically calculated between the first and fourth CMAP in a train of low frequency RNS. Decrement greater than 10% is abnormal in many laboratories.

Facilitation is ideally elicited with 10 seconds of isometric MVC in the context of low frequency RNS. A pre-exercise RNS train is initially delivered to establish a stable baseline and to assess for decrement. After 10 seconds of isometric MVC, a second train of RNS is delivered. The amplitude of the first post-exercise CMAP is compared with the first CMAP in a baseline, pre-exercise RNS train.

There are numerous opportunities for technical error in RNS testing, and rigorous inspection of each train of actual CMAP waveforms is necessary to prevent reporting error. Pseudofacilitation may follow high frequency RNS or muscle shortening with inadequate immobilization. Actual disease generates a regular, orderly decline in CMAP amplitudes by the fourth or fifth stimulus. RNS testing findings should be reproducible after appropriate rest periods.
**Needle Electromyography**

The needle electrode examination (NEE) is always abnormal in some fashion in the presence of neuromuscular weakness. During the NEE, intramuscular needle electrodes are used to record electrical potentials from muscle fibers. Potentials may arise from individual muscle fibers and from groups of muscle fibers. The motor unit action potential (MUAP) represents the summation of the single muscle fiber action potentials arising from fibers of a single motor unit. Most routine electromyographic studies utilize either concentric or monopolar needle electrodes. In concentric needles, the recording surface is an elliptical planar surface with an area of about 0.2-0.9 mm. Monopolar needles have a conical recording surface with an area of approximately 0.14-0.21 mm. The concentric needle has directional recording characteristics due to the shielding effect of the cannula. Monopolar needle electrodes have a relatively larger, nondirectional, spherical recording field, and MUAPs recorded with monopolar needles are therefore larger in amplitude and more complex than those recorded with concentric needles.

During the NEE, insertional activity is generated by mechanical depolarization of muscle fibers with both negative and positive spikes occurring with needle electrode insertion and movement. This activity stops almost immediately after needle movement ceases. Insertional activity may be increased when muscle is denervated or in myotonic disorders. Reduced insertional activity may occur with fibrous or fatty replacement of muscle fibers resulting from endstage neuropathy or myopathy, during contractures in myophosphorylase or phosphofructokinase disease. Muscle fibers within 1 mm of the electrode recording surface determine the morphology of the main spike component of the MUAP, and only 1-3 muscle fibers within 500 µm of the recording surface determine peak amplitude of the MUAP. With advanced reinnervation, increased fiber density is reflected as increased MUAP amplitude. In myopathy, MUAP amplitude may be reduced in areas of reduced fiber density or increased with fiber hypertrophy. MUAP duration is largely determined by activity of muscle fibers within 2.5 mm of the recording electrode surface. The complexity and shape of the MUAP waveform is determined by the synchrony of muscle fiber potentials reaching the electrode recording surface, that in turn is related to the position of the electrode with respect to the endplate region and to fiber diameter variation. In most normal muscles, less than 15% of MUAPs exhibit more than four phases (baseline crossings plus one).

**Abnormal Spontaneous Activity**

Fibrillation potentials reflect nonvolitional, individual muscle fiber potential discharges. They appear as brief (1-5 ms) biphasic or triphasic spikes with amplitude ranging from 20-250 µV and a regular firing rate ranging from 0.5-15 Hz. Positive sharp waves (PSWs) have a distinct biphasic waveform with initial sharp positivity. PSWs are actually fibrillation potentials. Their distinct morphology results from the position of the recording electrode with respect to the injured region of the muscle fiber where the muscle fiber potential fails to propagate beyond the recording electrode. Fibrillation potentials arise within 48 hours of denervation or may develop up to 3 weeks later in muscles distant to a nerve injury. They may also be seen in myopathies where the endplate region becomes disconnected from the motor nerve, such as in inflammatory or necrotizing myopathies, in myopathies associated with fiber splitting, or in myopathies with muscle fiber regeneration.

Myotonic discharges also represent spontaneous, nonvolitional discharges of individual muscle fibers presenting as trains of 20-300 µV positive spikes that wax and wane in amplitude and frequency. The loudspeaker output in myotonia resembles a revving motorcycle. Myotonic discharges are observed in dystrophic and nondystrophic myotonic disorders, inflammatory myopathy, Pompe disease, toxic myopathies, and are occasionally seen in severe axonal neuropathies and radiculopathies.

Complex repetitive discharges (CRDs) are spontaneous, synchronous discharges from groups of muscle fibers from nearby motor units. CRDs arise from ephaptic activation of adjacent muscle fibers that discharge in a regular sequence. The resulting discharge has a regular, complex morphology with a machinery-like sound with abrupt onset and offset. CRDs may be observed in chronic neuropathic or myopathic processes. Fasciculation potentials represent spontaneous single MUAP discharges without pattern or rhythm. Myokymic discharges are spontaneously firing, grouped MUAPs that fire in a repetitive pattern of regular bursts. Several MUAPs may fire within each group, and the firing rate within each group may range from 40-80 Hz. The frequency of the bursts ranges from 0.1-10 Hz. The sound of the discharges has been likened to marching soldiers. Myokymic discharges may be seen following head and neck or brachial/lumbar plexus radiation, in chronic radiculopathy or neuropathy, in the head and neck region with brainstem tumors, and in multiple sclerosis.

In neuromyotonia, another form of spontaneous MUAP firing, MUAPs fire at very high frequencies of 100-300 Hz. The firing may be sustained or may occur in a bursting pattern. Neuromyotonia is rare and can be observed in peripheral nerve hyperexcitability syndromes, including potassium channelopathies such as Morvan’s syndrome and tetany.

As noted above, the MUAP represents the summation of the muscle fiber action potentials arising from fibers of a single motor unit. MUAP morphology is determined by the type of electrode used and by the position of the recording surface with respect to the muscle fibers composing the motor unit. Normal MUAP morphology and firing patterns are altered in neuromuscular disease. Muscle fibers within 1 mm of the electrode recording surface determine the morphology of the main spike component of the MUAP, and only 1-3 muscle fibers within 500 µm of the recording surface determine peak amplitude of the MUAP. With advanced reinnervation, increased fiber density is reflected as increased MUAP amplitude. In myopathy, MUAP amplitude may be reduced in areas of reduced fiber density or increased with fiber hypertrophy. MUAP duration is largely determined by activity of muscle fibers within 2.5 mm of the recording electrode surface. The complexity and shape of the MUAP waveform is determined by the synchrony of muscle fiber potentials reaching the electrode recording surface, that in turn is related to the position of the electrode with respect to the endplate region and to fiber diameter variation.

MUAP stability is a reflection of the status of neuromuscular transmission. In an unstable MUAP with a neuromuscular transmission defect or immature reinnervation, there are moment to moment changes in the number and synchrony of muscle fiber action potentials that summate to form the MUAP. These moment to moment changes are manifest as changes in the pitch of the MUAP transmitted by the loudspeaker or as changes in the configuration of the MUAP displayed by the oscilloscope.
MUAP recruitment reflects the number of additional MUAPs that discharge as the firing rate of an initial MUAP increases with additional muscle activation. Under normal circumstances, the recruitment frequency or firing rate of a MUAP when a second MUAP is recruited is 8-10 Hz in limb muscles and up to 16 Hz in cranial muscles. With muscle denervation, additional MUAPs may not be available to increase muscle contraction force, so the surviving motor neurons increase their firing frequency beyond 10 Hz. The recruitment ratio refers to the rate of MUAP firing of a single MUAP relative to number of activated MUAPs. This ratio is less than five in normal muscles. Reduced recruitment, with an increased recruitment frequency and reduced recruitment ratio, is seen in neurogenic disorders or in endstage myopathy. In early or increased recruitment, more MUAPs fire than normal to generate a given degree of muscle contraction force. Recruitment frequency and ratios are normal. Early recruitment is observed in myopathy and can only be recognized if the amount of force generated by the patient is known.

The interference pattern is assessed during maximal muscle contraction. Under normal circumstances, the interference pattern is termed “full,” so that individual MUAPs cannot be discerned on the oscilloscope. When the interference pattern is incomplete, the MUAP recruitment and/or activation are reduced. Thus, an incomplete interference pattern may arise from denervation or from a suprasegmental process such as corticospinal or extrapyrimidal disease, apraxia, or reduced effort due to amotivation or pain. If activation is reduced to the degree that MUAP firing rates never exceed 10 Hz, recruitment cannot be assessed.

**Evolution of Needle Examination Findings in Neuropathic Disease**

In neuropathic disease causing weakness, NEE acutely reveals reduced recruitment of morphologically normal MUAPs. After approximately 2-4 weeks, abnormal spontaneous activity in the form of fibrillation potentials evolves. As a reflection of early reinnervation, increased MUAP duration, polyphasia, and instability may be observed around 2 months after neuropathic injury. As the reinnervation process progresses, recruitment remains reduced owing to the reduced number of motor neurons, but the amount of fibrillation potentials decreases, and MUAP stability improves. MUAP polyphasia decreases though duration remains increased.

**ELECTRODIAGNOSTIC APPROACH IN NEUROMUSCULAR WEAKNESS**

**Establishing the Distribution of Disease**

After formulating an anatomical hypothesis and differential diagnosis based on the history and clinical findings, testing should begin in the clinically involved limbs and, where feasible, recording from the weak muscles as directed by the history and physical findings. In order to establish the distribution of disease, the abnormal findings should be surrounded by normal findings, a process known as bracketing. Thus, when a NCS is abnormal, an analogous nerve in the same limb and the same nerve in the contralateral limb should be studied. For example, in a patient with right lateral hand numbness, differential diagnoses would include a median neuropathy at the wrist, a proximal median neuropathy, a lateral cord or upper trunk brachial plexopathy, and a C6 radiculopathy. If the right median motor distal latency were prolonged, a comparison should be made to the right ulnar motor conduction study and to the left median motor conduction study. This approach will determine whether NCS findings are focal (as in mononeuropathy with focal compression or conduction block), isolated to a limb (plexopathy or radiculopathy), multifocal with involvement of more than one limb, widespread with involvement of upper and lower limbs, or diffuse with uniform involvement of all limbs.

Similarly, when the NEE yields abnormal findings in a muscle, additional muscles should be sampled in order to bracket or surround the abnormal findings with normal ones. For example, in a C6 radiculopathy, the abnormal findings in the C6 myotome should be surrounded by normal findings in the C5 and C7 myotomes.

**Timing of Studies**

Although EDX studies can be performed at any time, studies in acute peripheral nerve disease may be misleading if the process of Wallerian degeneration is incomplete. Following nerve injury, CMAP amplitudes do not reach a minimum for up to 9 days, and SNAP amplitudes may not reach a nadir until 10-11 days post injury. Along with an apparently intact SNAP, an apparent motor conduction block may be observed if the front of Wallerian degeneration lies between the distal and proximal stimulation sites. In addition, it may take as long as 3 weeks for PSWs and fibrillation potentials to develop in all muscles innervated by a diseased or injured peripheral nerve. Thus, it is sometimes optimal to delay EDX assessment for 3 weeks after nerve injury in order to document the full complement of abnormal findings. However, in possible GBS, early findings and exclusion of other motor unit disorders are important for directing management, so expeditious assessment of such cases is appropriate.

**REFERENCES**

Peripheral neuropathy is a commonly encountered disorder evaluated by primary care physicians and neurologists in the community. Peripheral neuropathy can be subdivided into three types: mononeuropathy, mononeuropathy multiplex or mononeuritis multiplex, and polyneuropathy, based on the involvement of a single nerve, multiple single nerves, or many nerves in a symmetric length-dependent fashion. This manuscript will focus on the evaluation of patients with diffuse symmetric polyneuropathies.

CLINICAL PRESENTATION AND ETIOLOGIES

The prevalence of polyneuropathy is approximately 2.4% of the population in midlife, but rises to 8% in individuals older than 55 years. A careful history, physical examination, electrodiagnostic (EDX) testing, and laboratory testing reveals a cause in 74-82% of patients.

The clinical presentation of polyneuropathy usually obeys a sensory and motor length-dependent pattern that make the diagnosis relatively easy once the history has been elicited and the examination performed. Patients often state their condition began with numbness and paresthesia of the toes and soles of the feet and, over time, the symptoms advance proximally to affect the foot and ankle. Other descriptors include lack of feeling, woody sensation, sharp jabbing pain, electric shocks, sharp pains, and icpick pain. Often, the first motor symptom is gait instability, particularly walking in the dark or maintaining balance when the eyes are closed. As the disease advances, patients develop footdrop and frequent falls. Cramps are common, particularly in the distal legs. When the process progresses to the knees, patients often begin to experience hand weakness and dropping of items. Atrophy in the hands and feet is common when the polyneuropathy is severe or longstanding. Somatic neuropathies of the sensory and motor nerves are commonly accompanied by involvement of the autonomic fibers that can manifest as lack of sweating, change in skin color, orthostatic symptoms, change in bowel or bladder habits, and erectile dysfunction.

The neurologic examination in most neuropathies shows a distal gradient loss from the toes to the more proximal legs and, as the disease advances, from the fingertips to the wrists or forearms. The findings are relatively symmetric and any major asymmetry suggests a superimposed radiculopathy of single or multiple roots, a plexopathy, a spinal cord process, or a brainstem or cerebral cortex lesion. If the large sensory fibers are primarily affected, there is greater loss of vibration, light touch, and joint position sense than small-fiber functions of pain, pin prick, and cold perception. In most neuropathies, both large and small fibers are affected. Strength is lost in a similar pattern from the toes to the ankles, and from the intrinsic hand muscles to the finger flexors and wrist extensors and flexors. In inherited neuropathies and longstanding neuropathies, it is common to find high arched feet, hammertoes, and pronounced distal more than proximal atrophy, giving rise to the term inverted champagne bottle legs. Reflexes are diminished or lost in a predictable fashion. Ankle reflexes are lost first, followed by the knee reflexes, brachioradialis, and lastly the biceps brachii and triceps reflexes. If autonomic involvement
is present, the examiner may observe distal extremities that are cold or too warm, erythematos or blanche color changes, shiny skin, loss of hair over the feet and distal shins, dystrophic nails, lack of sweating in the axilla and groin region, and dry mouth, eyes, and mucosa.

When first evaluating a patient with polyneuropathy, it is a good practice to ask specific questions about prior diseases, lifestyle, and occupational exposure that may give a clue to the diagnosis. Questions should be asked about diabetes, alcohol abuse, vitamin deficiencies, dietary habits, use of over the counter drugs, zinc consumption, gastric bypass surgery, medications prescribed in the past (especially those used long term), human immunodeficiency virus (HIV), family history of neuropathy, foot deformities in the family, amyloidosis, thyroid disease, chronic renal and liver disease, malignancy, chemotherapeutic agents, connective tissue disorders, recreational use of substances, and exposure to heavy metals, industrial agents, herbicides, and pesticides.

Table 1 lists etiologies for polyneuropathy classified by type. As is the case in any classification, some disorders are more difficult to classify and some are so rare as to minimize the need to place them in a broad table.

<table>
<thead>
<tr>
<th>Table 1. Etiologies for Polyneuropathies</th>
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<tbody>
<tr>
<td>Endocrine: diabetes mellitus, hypothyroidism, hyperthyroidism</td>
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<tr>
<td>Alcohol abuse</td>
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<tr>
<td>Nutritional deficiencies: B1, B3, B6, B12, folic acid, and gastric bypass surgery</td>
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<tr>
<td>Vitamin excess: pyridoxine</td>
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<td>Metabolic: uremia, liver disease, porphyria</td>
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<td>Sarcoïdosis</td>
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<td>Connective tissue disorders: SLE, RA, Sjogren’s Syndrome, polymyositis nodosum</td>
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<tr>
<td>Vasculitis</td>
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<tr>
<td>Amyloidosis: secondary and familial</td>
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<tr>
<td>Genetic: Charcot-Marie-Tooth Disease and other inherited neuropathies</td>
</tr>
<tr>
<td>Inflammatory: GBS, CIDP, plasma cell dyscrasias, HIV infection, Lyme Disease, other infectious causes</td>
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<tr>
<td>Toxic: Industrial, therapeutic, chemotherapeutic agents, tacrolimus, heavy metal poisoning</td>
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<tr>
<td>Paraneoplastic: carcinoma, lymphoma, leukemia</td>
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<tr>
<td>Porphyria</td>
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<tr>
<td>HIV infection and anti-retroviral therapy</td>
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<tr>
<td>Critical illness polyneuropathy</td>
</tr>
</tbody>
</table>

SLE = systemic lupus erythematosus, RA = rheumatoid arthritis, GBS = Guillain-Barré syndrome, CIDP = chronic inflammatory demyelinating polyneuropathy. HIV = human immunodeficiency virus

From Donofrio.

Diabetes

Diabetes is the most common cause of polyneuropathy in the United States. Data from the National Institutes of Health and the Centers for Disease Control for the years 2005-2006, using interview techniques, and fasting and 2-hour glucose measured in subsamples, report that the crude prevalence of diabetes is 12.9% in patients over the age of 20 years. Forty percent of those patients were undiagnosed diabetics. The crude prevalence of impaired fasting glucose is 25.7% and impaired glucose tolerance is 13.8%, with almost 30% of patients having one or the other. Over 40% of individuals had diabetes or prediabetes. The prevalence was twice as high for non-Hispanic blacks and Mexican Americans.

Determining the prevalence of diabetic neuropathy depends on the parameters used to establish the diagnosis. For example, the diagnosis can be based on symptoms, signs (sensory and reflex loss, weakness, or autonomic features), nerve conduction studies (NCSs) and needle examination (NE), nerve pathology, or skin biopsy results. The prevalence can also depend on whether the data are collected on inpatients or outpatients. The medical literature has reported the prevalence from 15-100%, depending on the diagnostic criterion and the characteristics of the population. The neurologic literature suggests that greater than 60% of patients with diabetes will have signs or EDX evidence of a polyneuropathy at some time in their illness. Pirart in 1973 published his data on the prevalence of polyneuropathy in diabetes after following 4,400 diabetics for decades. Approximately 8% had neuropathy at the time of diagnosis of diabetes, 40% after 20 years, and 50% at 25 years. Other authors feel those percentages underestimate the prevalence of diabetic neuropathy in the population. A neurologist not uncommonly establishes the diagnosis of diabetes when testing for glucose intolerance is ordered in pursuit of a cause for an unexplained neuropathy. Approximately 25% of patients with diabetic neuropathy will have neuropathic pain and its presence may be the impetus for referral to a neurologist.

Several classifications have been created for diabetic neuropathy. This author favors the classification by Dyck, in which neuropathy is separated into anatomical groupings of symmetric polyneuropathies, cranial neuropathies, asymmetrical proximal neuropathy, and asymmetrical neuropathy with symmetrical distal neuropathy.

**Alcohol Abuse**

Alcohol abuse remains a common cause of polyneuropathy, but probably not to the same degree as in decades past when the nutritional value of food and substance abuse were less known to the general public. The clinical presentation of alcoholic neuropathy may depend on whether the patient is also thiamine deficient. Alcoholic neuropathy without thiamine deficiency tends to cause a slowly progressive, predominantly sensory neuropathy affecting the small fibers. Conversely, alcoholic neuropathy with thiamine deficiency is more variable, giving rise to a larger spectrum of motor and sensory abnormalities. Putative mediators of the effect of alcohol on the peripheral nerve include acetaldehyde, protein kinase A, and protein kinase C. It is estimated that 10-15% of chronic alcoholics develop neuropathy. Abstinence from alcohol can prevent progression of the neuropathy, but it is the author’s experience that alcoholic neuropathy usually does not improve when alcohol consumption is stopped.
Connective Tissue Diseases

Polyneuropathies can be seen in patients with connective tissue diseases such as systemic lupus erythematosus, rheumatoid arthritis, Sjögren’s syndrome, and polyarteritis nodosa. Rarely, polyneuropathies can be detected in patients with Churg-Strauss syndrome, microscopic polyangiitis, Wegener’s granulomatosis, nonsystemic vasculitis of the peripheral nerve, and scleroderma (systemic sclerosis). In this author’s experience, Sjögren’s syndrome is the most common connective tissue disease seen in his clinic associated with polyneuropathy. Sjögren’s syndrome is a chronic inflammatory disorder characterized by diminished lacrimal and salivary gland function which gives rise to the Sicca syndrome of dry eyes and mouth. Sjögren’s syndrome can present as a sole connective tissue disorder or in association with other conditions, most commonly rheumatoid arthritis. Approximately 20% of patients with Sjögren’s syndrome will have a detectable antibody to the SSA (Ro) or the SSB (La) antigens in their blood at the time of diagnosis and 43% during followup over 10 years. A salivary gland biopsy is often needed to substantiate the diagnosis when serologic testing is negative or equivocal. Many types of neuropathies can be seen in Sjögren’s syndrome including motor, sensory, sensorimotor, or autonomic polyneuropathy, sensory ganglion neuronopathy, polyradiculoneuropathy, mononeuritis multiplex, trigeminal mononeuropathy (unilateral or bilateral), and other cranial neuropathies. The most common neuropathy is a symmetric sensory greater than motor axon loss polyneuropathy followed by a cranial neuropathy of the trigeminal, facial, or cochlear nerves.

Inherited Neuropathies

Inherited neuropathies are common and account for approximately 10% of neuropathies seen at large referral centers. Inherited neuropathies are often lumped together under the term Charcot-Marie-Tooth (CMT) disease, yet the latter term applies to an inherited motor greater than sensory neuropathy typically associated with foot deformities such as pes cavus. The disease can present as early as the first decade of life, but often is not diagnosed until later in life, and sometimes not until the sixth or seventh decade. In addition to foot deformities, patients often have atrophy of the feet and hands, areflexia, mild distal sensory loss, scoliosis, and other orthopedic abnormalities. Many autosomal dominant, recessive, and X-linked recessive forms have been reported, which has complicated the ordering of genetic testing in patients with CMT disease. Genetic tests are available for rarer causes of inherited neuropathies including congenital hypomyelinating neuropathy, hereditary neuropathy with propensity to pressure palsies, distal hereditary pure motor neuropathies, hereditary sensory and autonomic neuropathies, hereditary focal neuropathies, and giant axon neuropathy.

Medication-Induced Neuropathies

The list of medications that can cause polyneuropathy increases each year as new treatments are introduced for the management of cardiac diseases, neoplasia, infections, autoimmune, and necrotizing illnesses. The toxic effects of medications can act at several levels of the peripheral nerve including the anterior horn cell, as is the case for dapsone, the dorsal root ganglion, which is the mechanism for toxicity of several of the chemotherapeutic agents, the peripheral myelin, and the motor and sensory axon. The majority of medications cause dysfunction at the level of the peripheral axon. Table 2 lists medications for which there is a reported cause and effect association with polyneuropathy.

| Table 2. Medication-induced neuropathies classified by anatomic site of pathology |
|--------------------------------------|-----------------|
| Axonopathy                           | Paclitaxel      |
| Almitrine*                           | Phenelzine      |
| Amiodarone                           | Phenotoin       |
| Amitriptyline                        | Podophyllin     |
| Ara-C                                | Propafenone     |
| Bortezomib                           | Sulfiapyridine* |
| Carbimide*                           | Sulfaalazine    |
| Chloramphenicol                      | Statins         |
| Chloroquine*                         | Stavudine (d4T) |
| Cimetadine                           | Suramin         |
| Cloquinol                            | Tacrolimus      |
| Clofibrate                           | Thalidomide     |
| Colchicine                           | Tumor Necrosis Factor-alpha antagonists |
| Cyanate                              | Vancomycin*     |
| Cyclosporin                          | Vincristine     |
| Danosine (ddl)                       | Vinorelbine     |
| Dichloroacetate                      | Zalcitabine (ddl) |
| Disopyramide*                        | Anterior Horn Cell |
| Disulfiram                           | Dapson         |
| Docetaxel                            | Dorsal Root Ganglion |
| Efosfamide                           | Cisplatin       |
| Enalapril*                           | Carboplatin     |
| Ethambutol                           | Efosfamide      |
| Ethionamide                          | Etoposide (VP-16) |
| Eretinate                            | Oxaliplatin     |
| Fialuridine (FIAU)                   | Pyridoxine     |
| Fluoroquinolones                     | Hydralazine     |
| Glutathione                          | Gold           |
| Isoniazid                            | Glutethimide   |
| Lamivudine (3TC)                     | Isoniazid       |
| Lansoprazole                         | Gentamicin*     |
| Leflunomide                          | Griseofulvin   |
| Linezolid                            | Indomethacin   |
| Lithium                              | L-tryptophan contaminant |
| Mefloquine                           | Streptokinase* |
| Mercury                              | Suramin        |
| Methaqualone                         | Tacrolimus     |
| Metronidazole                        | TNF-alpha antagonists |
| Misonidazole                         | L-Tryptophan contaminant |
| Nitrofurantoin                       | Zimeldine      |
| Nitrous Oxide                        |                |

* isolated case reports From Donofrio.
Several medications deserve special mention. Amiodarone is a commonly prescribed medication for the treatment of cardiac arrhythmias. Amiodarone can cause a demyelinating neuropathy whose presentation resembles chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). The same drug can produce a motor and sensory axon loss neuropathy. The association between vincristine and polyneuropathy has been known for decades and is one of the best recognized chemotherapeutic agents to cause polyneuropathy. Cisplatin and paclitaxel are also common causes of polyneuropathy. Both agents affect the dorsal root ganglion, giving rise to sensory symptoms and gait ataxia. The effect is dose related. Coasting (further progression of the neuropathy after the medication is stopped) may occur following treatment with these chemotherapeutic treatments.

Nitrofurantoin is a bacteriostatic antibiotic that has been used to treat urinary tract infections for decades. It is prescribed frequently for use on a daily basis to suppress chronic and recurrent urinary tract infections. Some patients may take the medication for years without interruption. Nitrofurantoin can cause a mild to severe sensory greater than motor polyneuropathy which in some patients is irreversible.

Pyridoxine (vitamin B6) is an essential vitamin that has been consumed in large doses by individuals to aid in bodybuilding, and has been prescribed as a treatment for premenstrual syndrome, carpal tunnel syndrome, schizophrenia, fibromyalgia, autism, and hyperkinesis. Pyridoxine is almost always prescribed when isoniazid is given for treatment of tuberculosis or for a recently converted purified protein derivative test. Schauburg and colleagues reported a large cohort of patients who developed a severe sensory neuropathy after taking 2-6 grams of pyridoxine daily for 2-40 months. All patients showed profound loss of most sensory modalities and were areflexic. All patients improved when pyridoxine was stopped, and two patients experienced almost complete recovery after 2-3 years of followup. The authors concluded that vitamin B6 in high doses was probably toxic to the dorsal root ganglia. Although pyridoxine sensory neuropathy is most commonly observed in individuals taking large doses of the vitamin, toxicity can be observed in patients consuming much smaller doses.

Colchicine can cause not only a neuropathy, but also a myopathy. Thalidomide may cause a sensory polyneuropathy. It is being prescribed more commonly than in the past now that it is recognized to be an effective treatment for several dermatologic conditions, multiple myeloma, HIV infections, and rheumatologic disorders.

**Statins**

Statins cause polyneuropathy infrequently (in less than 1% of patients), but its potential neurotoxicity must be recognized when no other etiology is found for a patient referred for an idiopathic polyneuropathy. The statins are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, an enzyme that regulates the synthesis of cholesterol. In 1994, Jacobs reported the development of a sensory polyneuropathy in a patient who was treated with lovastatin for 2 years. The patient’s symptoms abated when lovastatin was discontinued, but returned within 2 weeks when pravastatin was substituted for lovastatin.

Substitution of one statin that causes a polyneuropathy for another may not prevent the reoccurrence of a drug-induced neuropathy. Ziajka and Wehmeier reported a patient who developed a neuropathy after taking lovastatin and whose symptoms returned when treated on separate occasions with simvastatin, pravastatin, and atorvastatin.

Some physicians have challenged the relationship between statins and the development of polyneuropathy. Others recognize the relationship to be low risk, but acknowledge that long-term exposure increases the chances for the neuropathy. One paper estimated the incidence of statin-induced neuropathy to be approximately 1 case per 10,000 patients taking statins; another manuscript estimated 60 cases per 100,000.

**Polyneuropathies from HIV Infection and Highly Active Antiretroviral Therapy**

Polyneuropathies are associated with HIV infection and highly active antiretroviral therapy drugs such as the nucleoside reverse transcriptase inhibitors, zalcitabine, stavudine, and didanosine. The types of neuropathy detected in patients with active HIV infection include a distal sensory polyneuropathy, acute inflammatory demyelinating polyneuropathy (AIDP), CIDP, and mononeuritis multiplex. As the prevalence of HIV infection rises as patients live longer because of the effectiveness of treatment, the number of patients with HIV-related polyneuropathy will likely rise. For this reason, it is wise to check the HIV status of patients when initial screening does not reveal a cause.

**Industrial and Environmental Agents**

Table 3 lists common industrial and environmental agents that have been associated with causing neuropathy. Most of them are rare. Arsenic poisoning can lead to an acute polyradiculoneuropathy which clinically looks strikingly similar to the AIDP form of Guillain-Barré syndrome (GBS). Patients present with a gastrointestinal illness of vomiting, nausea, and diarrhea that is followed by a subacute ascending sensory and motor process producing weakness, areflexia, a severe length-dependent sensory loss, and autonomic involvement. Patients typically have other organ involvement such as cardiomyopathy, anemia, rash, hepatitis, and encephalopathy that should clue the physician to the unlikelihood of classic GBS. Testing for arsenic in the urine is more sensitive than blood levels, particularly several days after the poisoning. Mees’ lines are found in the fingernails of patients with acute arsenic poisoning, but the lines commonly do not appear until 6-8 weeks after acute poisoning. Low level chronic arsenic poisoning results in a painful sensory and motor length-dependent polyneuropathy that is indistinguishable from most other chronic neuropathies. Lead intoxication can cause a motor and sensory length-dependent neuropathy or the clinical constellation of bilateral wrist and foot drop.
B12 Deficiency

B12 deficiency as a cause of polyneuropathy remains a common phenomenon. Patients typically present with a sensory neuropathy and a myelopathy called subacute combined degeneration (SCD), a term that is descriptive for the pathology of the dorsal column, cortical spinal tract, and peripheral nerve. Patients typically have loss of vibration and joint position sense in the toes and ankles, hyperreflexia in the upper extremities and knees, and absent ankle reflexes. Neuropathologically, patients have a large-fiber neuropathy and atrophy of the dorsal column and the corticospinal tracts. Hematologic studies show a megaloblastic anemia with an elevated mean corpuscular volume and hypersegmented polymorphonuclear white blood cell (WBC) count. Serum levels of B12 below 100 pg/ml are diagnostic of B12 deficiency and levels between 100-200 pg/ml are suggestive. Levels between 200-300 pg/ml should be considered suspicious for the diagnosis and should lead to further testing if the patient has a polyneuropathy. Elevated methylmalonic acid and homocysteine levels help to support the diagnosis. In years past, it was common to order a Schilling test to assess B12 absorption and the level of dysfunction in the gut. This practice has been supplanted by testing for methylmalonic and homocysteine levels. Treatment with B12 injections is thought to arrest disease progression and, in some instances, reverse some of the symptoms and signs of SCD. Copper deficiency is a recently described disorder which bears many similarities to SCD, although the condition is much less common than B12 deficiency. If the disease is severe or untreated for long periods, patients manifest lower extremity paresthesia, leg weakness, gait ataxia, and spasticity. Similar to SCD, patients have a myelopathy and a peripheral neuropathy, clinically and electrophysiologically. The anemia associated with copper deficiency is microcytic and is associated with neutropenia and sometimes pancytopenia. Intravenous copper treatment reverses the hematologic, but not the neurologic, manifestations of the illness. Several cases of copper deficiency neuropathy and anemia have been described in patients who have zinc toxicity, as high zinc levels lead to copper deficiency. Some denture creams are known to contain large amounts of zinc and some patients were using large amounts of denture cream to secure their dentures. For this reason, patients with low copper levels should be screened for zinc toxicity.

Paraneoplastic Neuropathy

Paraneoplastic neuropathy refers to a neuropathy associated with the presence of a neoplasm in other areas of the body (a remote effect phenomenon). The most common paraneoplastic neuropathy is a length-dependent, sensory greater than motor polyneuropathy, which is indistinguishable from other conditions giving this clinical picture. The less common, but earlier reported neuropathy, is the dorsal root ganglionopathy first reported by Denny Brown in 1948. This neuropathy manifests as a pure sensory neuronopathy affecting large and small fibers. The neuropathy often precedes the detection of the tumor by months to years. The neuropathy may be prominent enough to cause severe ataxia of gait and, in the severest form, choreoathetosis of the hands and arms. The majority of paraneoplastic sensory neuropathies are secondary to lung carcinomas. Approximately 65% are due to small cell (oat cell) carcinoma of the lung and another 13% from anaplastic, bronchial, and squamous cell carcinoma of the lung. Other neoplasms rarely cause a sensory neuronopathy, but it has been associated with Hodgkin’s lymphoma, reticulum cell sarcoma, and esophageal, colon, breast, uterus, and synovial tumors.

Paraproteinemias

Paraproteinemias is a common association with polyneuropathy. Kelly and colleagues showed that approximately 10% of patients with previously undiagnosed neuropathies were found to have a monoclonal protein. Table 4 lists the diseases that produce a paraprotein and each should be investigated in a patient with neuropathy and a paraproteinemia. The pathology can be axon loss or demyelinating. Monoclonal gammopathy of uncertain significance accounts for the etiology in more than 50% of these patients. A rare, but interesting condition is POEMS syndrome. The latter eponym describes a polyneuropathy in a patient with organomegaly, endocrinopathy, a monoclonal protein, and skin changes.

Patients with monoclonal proteins and a severe demyelinating neuropathy should be screened for osteosclerotic neuropathy, a condition associated with single or multiple osteosclerotic lesions in the spine, pelvis, and the long bones of the arms and legs. The clinical and EDX features of the neuropathy suggest the diagnosis of CIDP. The neuropathy may precede the detection of the monoclonal protein. Treatment depends on whether the condition is solitary or multiple and the polyneuropathy may partially reverse after radiation therapy or chemotherapy.

<table>
<thead>
<tr>
<th>Table 3. Industrial and environmental toxic neuropathies</th>
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<tbody>
<tr>
<td><strong>Heavy Metals</strong></td>
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<tr>
<td>Arsine</td>
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<td>Cadmium</td>
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<td>Mercury</td>
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<td>Lead</td>
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<td>Thallium</td>
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<tr>
<td>Hexacarbons</td>
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<tr>
<td>N-hexane</td>
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<td>Methyl butyl ketone</td>
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<table>
<thead>
<tr>
<th>Table 4. Paraproteinemias associated with polyneuropathy</th>
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<tbody>
<tr>
<td>Monoclonal gammopathy of undetermined significance</td>
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<tr>
<td>Multiple myeloma</td>
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<tr>
<td>Smoldering myeloma</td>
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<tr>
<td>Osteosclerotic myeloma</td>
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<tr>
<td>POEMS syndrome</td>
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<tr>
<td>Waldenstrom’s macroglobulinemia</td>
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<tr>
<td>Systemic amyloidosis</td>
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<tr>
<td>Cryoglobulinemia</td>
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<tr>
<td>Lymphoma</td>
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</tbody>
</table>

POEMS syndrome = polyneuropathy with organomegaly, endocrinopathy, a monoclonal protein, and skin changes.
**Gastric Bypass Surgery**

Neuropathies have been associated with nutritional factors, a relationship known for decades. A recent association is the neuropathy that arises after bariatric surgery. Thaisetthawatkul and colleagues reported their results from a review of 435 patients undergoing bariatric surgery at Mayo Clinic. A polyneuropathy was observed in 27 patients, a mononeuropathy in 39, and a radiculoplexopathy in 5. Risk factors for the neuropathy included the rate and amount of weight loss, the presence of prolonged gastrointestinal symptoms, failure to attend a nutrition clinic after surgery, a reduced albumin or transferrin after surgery, postoperative surgical complications requiring hospitalization, and a jejunooileal bypass procedure.

**Inflammatory Polyradiculoneuropathies**

GBS is an acute or subacute polyradiculoneuropathy, typically observed in patients who were previously healthy. The disease most commonly begins 7-10 days after a seemingly benign viral infection of the respiratory or gastrointestinal system. The illness typically begins with paresthesias in the toes and feet which rapidly ascend proximally in the lower extremities and eventually to the distal upper extremities. Within a few hours to days, the patient experiences weakness that progresses in the same pattern. The weakness varies from mild to quadriplegia and, in approximately 30% of patients, to diaphragmatic weakness, respiratory failure, and intubation. In 40% of patients, the weakness is proximal greater than distal, in keeping with the radicular component of the inflammatory polyradiculoneuropathy. Autonomic involvement is not uncommon and can be manifested as unexplained bradycardia or tachycardia, hypotension or hypertension, profuse sweating, urinary retention, cool limbs, skin erythema, or blanching. Pain is observed in 40% of patients and tends to be localized to the lower back and posterior thighs.

The pathophysiology of GBS can vary from a pure demyelinating, motor more than sensory polyradiculoneuropathy, a pure axon loss neuropathy (acute motor axonal neuropathy [AMAN]), pure axon loss motor and sensory neuropathy, pure sensory, or autonomic neuropathy. Rare presentations of GBS include a paraparetic form, a pharyngeal-cervical-brachial form, and a form only affecting the upper extremities. Miller Fisher syndrome is a commonly diagnosed form of GBS in which patients develop ophthalmoplegia, areflexia, and ataxia over several days.

Laboratory studies that support the diagnosis of GBS are an elevated spinal fluid protein in the setting of few or no WBCs, (i.e., cytoalbumin dissociation), and abnormal EDX results which can vary from normal to peripheral nerves that cannot be stimulated. A common EDX picture is one of multifocal demyelination. In this setting, patients have prolonged distal latencies, slowed conduction velocities, temporal dispersion, partial to complete conduction block in motor nerves, and prolonged or absent F waves. The diagnosis of GBS requires a high level of diagnostic suspicion when the spinal fluid protein is normal and the EDX findings are not classic for the condition. Treatment of GBS within the first 30 days should entail either intravenous immunoglobulin (IVIg) or plasma exchange unless the patient is ambulatory. Both therapies are considered equally efficacious.

CIDP is often considered in the same category as GBS, as both diseases share EDX and spinal fluid similarities. The prevalence of CIDP is 2-5 per 100,000 people, similar to GBS. Considering the monophasic presentation of GBS and the chronicity of CIDP, CIDP populates more outpatient clinic visits than GBS at most large neuromuscular medical centers. CIDP is the diagnosis reached in approximately 20% of patients who initially have an undiagnosed neuropathy, and in 10% of patients referred to a tertiary care neurology clinic for presumed idiopathic neuropathy. CIDP evolves over 2 or more months and may be present for months to years before the diagnosis is established. In approximately 15% of patients, CIDP can have a more rapid subacute presentation that can resemble GBS. Patients have symmetric weakness in the arms and legs and, not uncommonly, the weakness is greater proximally than distally. Sensory findings are more common than in GBS, and tend to affect large more than small fibers. The nerve biopsy may show demyelination, inflammation, or both, but large studies of nerve biopsies in CIDP show both phenomena in fewer than 50% of patients. The spectrum of treatments for CIDP is broader than for GBS. Prednisone, IVIg, and plasma exchange have been shown to be effective in controlled studies. Other therapies have been tried such as azathioprine, cyclophosphamide, cyclosporine, mycophenylate mofetil, interferon, and rituximab with success in some patients. None of those immunosuppressants have been shown to be effective in large, placebo-controlled trials.

Approximately 15-20% of patients with CIDP have an associated monoclonal protein, usually of the immunoglobulin G or immunoglobulin A type. Treatment is usually similar to CIDP.

**Laboratory Testing of Polyneuropathy**

The goal of evaluating patients who present with polyneuropathy is to identify etiologies that are reversible or amenable to stabilization. Select tests may be used to detect and follow an illness, and genetic testing can be useful for counseling of patients, their siblings, and children. Testing in phases, based on the frequency and probability of a disorder, yields a diagnosis more quickly and without expending valuable patient resources. Recently, England and associates reported their findings on the value of ordering tests for the evaluation of polyneuropathy. They determined that a serum B12 with metabolites, blood glucose, and serum protein electrophoresis with immunofixation yielded the highest benefit when testing patients who presented with a polyneuropathy. The yield of other studies dropped off rapidly. This author advocates a three-phase approach to evaluating polyneuropathies, beginning first with a complete blood count test, comprehensive metabolic profile, B12, serum protein electrophoresis with immunofixation, sedimentation rate, and testing for glucose intolerance. If this testing does not lead to a diagnosis, the author suggests a B1 and B6 level, rheumatology screen, antinuclear antibody test, anti-SSA (Ro) and anti-SSB (La) antigens, and sometimes other studies for connective tissue diseases. The third phase of testing is HIV testing, angiotensin-converting enzyme level, paraneoplastic antibodies, 24-hour urine for heavy metals, a vitamin E and copper level, and testing for autoantibodies to axon and myelin proteins. Cerebrospinal fluid (CSF) testing is reserved for those patients who might have an inflammatory neuropathy such as CIDP or GBS, and in whom the diagnosis would be aided by this procedure.
Nerve biopsies are usually not necessary for the evaluation of the vast majority of patients with a distal length-dependent polyneuropathy. An etiologic diagnosis can be made in most patients without a tissue sample. Most often the sural nerve is biopsied, but the superficial peroneal nerve may be preferable in special circumstances, and the radial sensory nerve might be biopsied if symptoms are more prominent in the upper extremities. Some authors recommend obtaining adjacent muscle tissue when performing a sensory nerve biopsy as the two tissues sampled in the same surgical procedure increase substantially the yield for vasculitis. For this reason, biopsies of the superficial peroneal sensory nerve and the adjacent gastrocnemius muscle can be a good choice in patients where a tissue diagnosis is needed.

Table 5 lists the indications for sensory nerve biopsy based on this author’s review of the neurologic literature. The most common indication is a presumed or suspected vasculitis. A small fiber neuropathy can be verified by a sural or superficial peroneal sensory nerve biopsy, but may be more easily established using quantitative sudomotor axon reflex testing or skin biopsy for epidural nerve fiber density.

Table 5. Indications for nerve biopsy

<table>
<thead>
<tr>
<th>Vasculitis</th>
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<tr>
<td>Amyloidosis</td>
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<tr>
<td>Hansen’s disease (leprosy)</td>
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<tr>
<td>Metachromatic leukodystrophy</td>
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<tr>
<td>Fabry disease</td>
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<tr>
<td>Krabbe disease</td>
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<tr>
<td>Giant axonal neuropathy</td>
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<tr>
<td>Polyglucosan body disease</td>
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<tr>
<td>Tumor infiltration</td>
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<tr>
<td>Small fiber neuropathy</td>
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</table>

As the number of genetic defects in hereditary neuropathies increases, a need arises for an organized approach to ordering tests for inherited neuropathies. England and colleagues published a helpful algorithm for the logical progression of ordering genetic testing for patients with CMT and other suspected familial neuropathies. According to the algorithm, if an inherited neuropathy is suspected, the first tests to be pursued would be NCSs and NE. If the family history is positive, the neuropathy appears to be demyelinating, and the inherited pattern is autosomal dominant, then peripheral myelin protein 22 (PMP22) duplication testing should be ordered, and if negative, one would proceed to testing for myelin protein zero mutation and PMP22 mutation. The testing algorithm is different for recessive and sex-linked presentations and if the family history is negative.

The Role of Electrodiagnostic Testing

NCSs and NE are necessary and justifiable in many patients with polyneuropathy to help establish if a neuropathy is present, to determine whether the motor or sensory fibers are involved, and whether the process is axon loss, demyelinating, or both. EDX testing is also useful to document the areas of involvement (diffuse, focal, or multifocal), and whether the neuropathy documented by the NCSs parallels the clinical examination. The EDX evaluation is designed to test nerves suspected to be abnormal based upon the patient’s history and neurologic findings. Initial impressions are confirmed or altered, and the study is modified to accept or reject additional considerations until a final diagnosis is achieved. Thus, performing NCSs is usually a work in progress, with the goal to verify a polyneuropathy testing the fewest number of nerves. Since absent responses impart no information about the presence or absence of demyelination, information from proximal nerves in the legs and arms can often provide this data. Bilateral studies are performed on some nerves to document symmetry of the neuropathy and to eliminate the possibility of a superimposed multifocal process such as mononeuritis multiplex.

In performing NCSs, several principles of anatomy and physiology must be remembered. Lesions proximal to the dorsal root ganglia produce abnormalities detected on the sensory examination (often in a radicular pattern), but all sensory nerve conduction parameters such as amplitude and distal latency remain normal in those nerves subserving the areas of sensory loss. Abnormal sensory amplitudes imply peripheral involvement distal to the dorsal root ganglion either in the plexus, peripheral nerve, or digital nerves. Weakness and atrophy in combination with low motor amplitudes reflect abnormality of the lower motor neuron, but cannot localize...
the lesion more precisely. Additional evaluation is required to place the abnormality at the level of the motor neuron, nerve root, axon, neuromuscular junction, or muscle.

One of the goals in performing NCSs is to identify whether the primary pathophysiology is axonal degeneration or demyelination. Axonal degeneration results whenever the cell body (neuronopathy) or axon (axonopathy) is affected. Axon loss lesions produce reduced amplitudes (sensory or motor), yet cause little or no changes to the distal latency or conduction velocity. Amplitudes are reduced proportional to the amount of axonal loss, but conduction along intact axons is only reduced to the extent that large myelinated axons are lost.

Conduction slowing results from several processes, including loss of large axons, demyelination (hereditary or acquired), and altered sodium channels at the nodes of Ranvier. The amount of slowing after selective loss of large axons is relatively mild, whereas primary demyelination typically produces substantial slowing, depending on the severity and distribution of the demyelination. Most demyelinating neuropathies are associated with some superimposed axonal degeneration. When conduction slowing is identified, the EDX physician should determine whether an inherited or an acquired disorder exists. Hereditary disorders typically produce uniform involvement of the myelin sheath, uniform slowing in all fibers, and uniform slowing in all segments of the nerve, both proximally and distally. This slowing of conduction velocity is recorded in the setting of relatively preserved amplitudes and in the absence of abnormal temporal dispersion or conduction block. In NCSs, acquired demyelinating neuropathies characteristically produce multifocal and nonuniform abnormalities. Greater involvement of some fibers and fiber segments compared to others leads to long-duration compound muscle action potentials (CMAPs) with partial conduction block and differential slowing because of transmission failure along some axons. Abnormal dispersion of the CMAP and/or conduction block is observed when proximal sites are stimulated and the waveforms compared to those recorded on distal stimulation. Different waveform morphologies can be observed when the motor nerve is stimulated at multiple sites.

NEUROPATHY CLASSIFICATION BASED UPON EDX FINDINGS

The peripheral nerve responds in a limited number of ways to a pathologic insult. Those include axon degeneration, demyelination, and metabolic changes that alter nerve conduction. The classification of peripheral neuropathy that follows is based on the limited number of ways that peripheral nerves respond to disease and separates peripheral disorders into broad categories based upon the presence or absence of sensory abnormalities, motor abnormalities, and conduction slowing.

Motor or Motor Greater Than Sensory, Axonal Loss

The axonal form of CMT disease is known as hereditary motor sensory neuropathy type II (HMSN2) and is the prototype of the axonal motor greater than sensory neuropathy. In NCSs, motor amplitudes are reduced in the setting of normal or minimally slowed conduction velocities. Sensory responses are absent in about 50% of patients with HMSN2. When sensory responses are present, differentiating HMSN2 from a familial progressive muscular atrophy can be difficult. As expected, the NE demonstrates neurogenic changes which have a distal predilection (increased insertional activity, positive sharp waves and fibrillation potentials, and reduced recruitment of large amplitude motor units).

The hepatic porphyrias include acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria, all of which demonstrate overproduction of porphyrin precursors and porphyrins. Clinical abnormalities include the triad of abdominal pain, psychosis, and neuropathy. Porphyrin neuropathy resembles GBS with its subacute onset of weakness, areflexia, dysautonomia, and elevated CSF protein. Expected nerve conduction abnormalities include reduced CMAP amplitudes, essentially normal conduction velocities, fibrillation potentials, and decreased MUAP recruitment. Sensory responses occasionally are spared.

Other axonal motor greater than sensory neuropathies include AMAN, the motor axonal form of GBS, as well as a variety of toxic and drug-induced neuropathies, and the remote effect motor neuropathy associated with lymphoma or carcinoma. Vincristine toxicity typically produces a chronic axonal sensorimotor neuropathy, but occasionally results in rapidly progressive weakness with little increase in sensory involvement, resembling a pure motor neuropathy or neuronopathy. Table 7 lists neuropathies that tend to affect the motor axons only or motor more than sensory axons.

<table>
<thead>
<tr>
<th>Table 7. Motor or motor greater than sensory, axonal loss</th>
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<tr>
<td>Axonal form of Charcot-Marie-Tooth disease (hereditary motor sensory neuropathy type II)</td>
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<tr>
<td>Dapsone toxicity</td>
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<tr>
<td>Disulfiram toxicity</td>
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<tr>
<td>Acute motor axonal neuropathy</td>
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<tr>
<td>Acute motor sensory axonal neuropathy</td>
</tr>
<tr>
<td>Hyperinsulinism</td>
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<tr>
<td>Nitrofurantoin toxicity</td>
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<tr>
<td>Organophosphate poisoning</td>
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<tr>
<td>Porphyria</td>
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<tr>
<td>Paraneoplastic motor neuropathy (lymphoma or carcinoma)</td>
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<tr>
<td>Vincristine toxicity</td>
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</table>

Motor Greater Than Sensory, Uniform Conduction Slowing

Hereditary motor sensory neuropathy type I (HMSN1), also known as CMT disease, type I, is characterized by uniform demyelination (pathologically) and nerve conduction slowing (electrophysiologically). It represents the prototype of a uniformly demyelinating neuropathy. This inherited hypertrophic neuropathy presents in early adult life with distal weakness, areflexia, and foot deformities. Other clinical findings include palpably enlarged nerves, hammertoes and pes cavus, abnormal vibratory sensation in the toes, and hyporeflexia. Conduction velocities are markedly reduced, often as low as 25 ms or less.
In adults, reference values for motor conduction velocity typically exceed 50 ms in the arms and 40 ms in the legs. Conduction velocities less than 70% of the lower limit of normal are highly suggestive of demyelination or a membranopathy. They are inconsistent with axonal loss alone because the approximate conduction velocity of the smallest recordable myelinated axons spans the spectrum of 70-100% of the lower limits of normal. For this reason, an abnormality of the myelin sheath or the membrane must be present to account for the markedly reduced velocities. Pathologically, the distribution of demyelination in HMSN1 is uniform throughout the nerve. Thus, conduction velocity slowing is uniform from segment to segment. Abnormal temporal dispersion and partial conduction block, hallmarks of acquired multifocal demyelination, are not usually recorded. CMAP amplitudes and morphology remain unchanged between distal and proximal stimulation sites. Table 8 lists neuropathies that commonly present with motor more than sensory conduction velocity slowing that is uniform.

<table>
<thead>
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<th>Table 8. Motor greater than sensory, uniform conduction slowing</th>
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<tr>
<td>Amiodarone</td>
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<tr>
<td>Charcot-Marie-Tooth disease, type I (hereditary motor sensory neuropathy, type I)</td>
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<tr>
<td>Cytosine arabinoside</td>
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<tr>
<td>Dejerine-Sottas disease (hereditary motor sensory neuropathy, type III)</td>
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<tr>
<td>Hexacarbon toxicity</td>
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<tr>
<td>Perhexilene maleate adverse effect</td>
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<tr>
<td>Sodium channel blockers</td>
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Amiodarone toxicity is associated with a slowly progressive motor neuropathy in some patients, where conduction slowing in the range of 20-30 ms has been recorded. Abnormal temporal dispersion and partial conduction block are not features of this neuropathy. The motor abnormalities are associated with low amplitude sensory responses when the neuropathy is severe. In other patients, the EDX features of amiodarone-induced neuropathy are those of an axonal loss neuropathy. Neurotoxins that block sodium channels include tetrodotoxin, derived from the puffer fish, and saxitoxin, whose source is contaminated shellfish (red tide). Sodium channel blockade impedes the rapidly changing local currents needed to propagate saltatory nerve conduction. The effect of these neurotoxins is similar to that seen with cooling temperatures that slow conduction velocity. Motor amplitudes are reduced, but no abnormal temporal dispersion or partial conduction block is typically observed.

Several hexacarbon solvents and glues are implicated in causing neuropathy after occupational or recreational exposures. N-hexane and methyl butyl ketone are metabolized to 2, 5-hexanedione, the likely neurotoxic agent. The neuropathy is characterized by progressive distal sensory loss, reduced or absent reflexes, eventual weakness and atrophy, and sometimes autonomic dysfunction. Patients who voluntarily inhale n-hexane sometime develop a rapidly progressive motor greater than sensory neuropathy. Motor and sensory amplitudes are reduced and conduction slowed, suggestive of primary demyelination. However, in this case, the slowing is due to secondary myelin damage resulting from giant axonal swellings.

Motor Greater Than Sensory, Multifocal Conduction Slowing

Inflammatory demyelinating polyneuropathies are acquired immune diseases that include acute GBS, CIDP, and other chronic dysimmune neuropathies that mimic CIDP. CIDP is an example of a relatively common treatable and reversible neuropathy that was rarely recognized several decades ago. Because it may be associated with an underlying systemic illness (plasma cell dyscrasia, Waldenström's macroglobulinemia, gamma heavy chain disease, cryoglobulinemia, lymphoma, systemic lupus erythematosus, Castleman's disease, occult malignancy, and HIV infection), recognition of these conditions is important. These inflammatory demyelinating neuropathies typically present with progressive weakness, areflexia, decreased sensation, and elevated CSF protein. Table 9 lists many of the neuropathies that give a multifocal conduction slowing pattern.

<table>
<thead>
<tr>
<th>Table 9. Motor greater than sensory, multifocal conduction slowing</th>
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<tr>
<td>Arsenic (acute intoxication)</td>
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<tr>
<td>Guillain-Barré syndrome</td>
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<tr>
<td>Subacute inflammatory demyelinating polyneuropathy</td>
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<tr>
<td>Chronic inflammatory demyelinating polyneuropathy</td>
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<tr>
<td>Chronic dysimmune polyneuropathy</td>
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<tr>
<td>Monoclonal gammopathy of undetermined significance</td>
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<tr>
<td>Osteosclerotic myeloma</td>
</tr>
<tr>
<td>Multiple myeloma (substantial proportions are axonal)</td>
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<tr>
<td>Systemic lupus erythematos</td>
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<tr>
<td>Waldenström's macroglobulinemia</td>
</tr>
<tr>
<td>Gamma heavy chain disease</td>
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<tr>
<td>Cryoglobulinemia</td>
</tr>
<tr>
<td>Castleman's disease</td>
</tr>
<tr>
<td>Lymphoma</td>
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<tr>
<td>Carcinoma</td>
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<tr>
<td>Human immunodeficiency virus infection</td>
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<tr>
<td>Multifocal motor neuropathy with conduction block</td>
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</tbody>
</table>

Abnormal temporal dispersion and/or partial conduction block of CMAP responses, slowed nerve conduction velocities, and prolonged distal latencies and F-wave latencies characterize the acquired demyelinating neuropathies (see Figure 1). In general, emphasis and importance should not be placed on mild conduction slowing, as the latter is often observed in axon loss conditions. The EDX evaluation should be sufficiently extensive to include motor nerves with reasonably preserved distal amplitudes. If responses cannot be elicited from motor nerves in the legs and distal upper extremities, the physician or technician should test proximal motor nerves such as the musculocutaneous, spinal accessory, and femoral. In general, conduction velocities less than 70% of the lower limit of normal define primary demyelination. In some patients, early in the illness, marked prolongation of distal latencies will be recorded at a time when routine nerve conduction velocities are normal or only slightly slowed. Absent F responses alone may be recorded in the first week of an acute demyelinating neuropathy and may be the earliest finding in GBS. The NE has a secondary role in the assessment of demyelinating polyneuropathies and is performed to document the degree of
accompanying axon loss, the distribution of denervation, and the duration of the disease. It is a relatively insensitive measure of severity and prognosis. In GBS, the NE is usually not performed until the third or fourth week of the illness, at a time when axon loss, if present, would be recordable.

Figure 1: Nerve conduction study of the tibial motor nerve demonstrating temporal dispersion between popliteal stimulation and ankle stimulation in a patient with CIDP.

Acute arsenical neuropathy is one component of a systemic illness characterized by nausea, vomiting, diarrhea, dermatitis, cardiomyopathy, pancytopenia with basophilic stippling, and abnormal liver function tests. The temporal profile of a gastrointestinal illness followed by a rapidly evolving neuropathy suggests the diagnosis of GBS and acute arsenic poisoning is frequently misdiagnosed as GBS. Initial EDX studies in acute arsenic poisoning show reduced conduction velocity, increased temporal dispersion, partial conduction block, and low amplitude or absent sensory responses. Serial studies usually demonstrate a dying-back neuropathy with progressive axonal degeneration, suggesting that the initial EDX findings probably relate to generalized axonal failure rather than a primary demyelinating process. Clinically, acute arsenic poisoning evolves into a severe, irreversible, chronic motor and sensory polyneuropathy with prominent weakness and neuropathic pain.

Sensory, Axonal Loss (Neuropathy or Neuronopathy)

Sensory symptoms and signs are usually the earliest features of most sensorimotor neuropathies. The most common axon loss sensory neuropathies or neuronopathies are listed in Table 10. These disorders typically present subacutely with paresthesias, impaired vibration and joint position sensation, and areflexia. As the diseases progress, patients often develop impaired coordination, involuntary movements, and gait disorders, features betraying large fiber sensory dysfunction in the limbs.

Pyridoxine can produce a neuropathy when deficient in the diet or when taken in excess. Patients who place great importance on vitamin supplementation may take pyridoxine in megadoses, and sometimes large doses of vitamins may be used to treat premenstrual syndrome, carpal tunnel syndrome, schizophrenia, fibromyalgia, autism, and hyperkinesis. Dose-related neurotoxicity can develop from long-term cumulative exposure or after short-term administration of large doses. Sensory loss may be complete and irreversible, and may be associated with choreaathetoid movements. Cisplatin produces a dose-related sensory neuronopathy that is indistinguishable from the paraneoplastic sensory neuronopathy associated with small cell lung carcinoma and antineuronal antibodies. In many patients, the unusual electrophysiologic pattern develops of normal motor studies and completely absent sensory responses (in the arms and legs). This pattern of abnormalities is atypical for an early sensorimotor neuropathy (where one would expect to see some motor abnormalities) and is more in keeping with a sensory neuronopathy from pathology in the dorsal root ganglia diffusely.

Table 10. Sensory, axonal loss

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Pyridoxine toxicity</td>
</tr>
<tr>
<td>Congenital neuropathy</td>
<td>Sjögren’s syndrome</td>
</tr>
<tr>
<td>Metronidazole toxicity</td>
<td>Styrene poisoning</td>
</tr>
<tr>
<td>Paraneoplastic sensory neuronopathy</td>
<td>Thalidomide</td>
</tr>
</tbody>
</table>

Sensory Greater Than Motor, Axonal Loss

This classification constitutes the largest number of neuropathies. Many of the sensorimotor neuropathies present with predominantly sensory abnormalities and mild, often subclinical, motor changes (Table 11). Early in the polyneuropathy, the latter may be apparent on NE only, without clinical evidence of weakness. These neuropathies include most toxic and metabolic neuropathies, nutritional disorders, connective tissue disorders, and some degenerative conditions. Most toxic and metabolic polyneuropathies are characterized by distal axonal degeneration (dying back) of sensory and motor axons. Most are physiologically similar and cannot be distinguished without laboratory testing. Sensory symptoms and signs predominate. Weakness and atrophy of distal muscles often develop later in the illness. In most patients with a sensorimotor axonal loss neuropathy, sensory amplitudes are abnormal early in the course of disease at a time when sensory distal latencies and conduction velocities are normal or slightly abnormal. CMAP amplitudes become abnormal later in the illness, first in distal leg nerves. Conduction velocities, motor distal latencies, and F-wave latencies remain essentially normal unless extensive axon loss ensues which affect the large diameter motor fibers. On NE, increased insertional activity, fibrillation potentials, positive waves, and decreased recruitment of reinnervated motor units are seen distally.
Mixed Sensory and Motor, Conduction Slowing and Axonal Loss

In early symmetric diabetic neuropathy, sensory symptoms and signs usually predominate over motor complaints. Weakness eventually develops, usually manifesting initially as toe and ankle dorsiflexion impairment and later progressing more proximally.

Even asymptomatic, neurologically normal diabetic patients can manifest nerve conduction abnormalities. Conduction velocities at the lower limit of normal are common. With increasing severity, CMAP amplitudes become reduced and nerve conduction velocities become slower. Abnormal temporal dispersion and partial conduction block to a small degree can be recorded, but are not prominent. Some patients with isolated sensory abnormalities, and most patients with generalized sensorimotor diabetic neuropathy, have EDX features reflecting active and chronic denervation distally.

 Patients with renal failure independent of diabetes mellitus can develop a sensorimotor neuropathy characterized by low amplitude motor and sensory responses, sometimes in association with pronounced conduction slowing. This is most apparent in patients who had end-stage renal disease (ESRD). The magnitude of slowing is greater than expected from axonal loss alone, and chronic demyelination and remyelination plus membrane changes contribute to the slowing. Although NCSs play an important role in making the diagnosis of ESRD neuropathy, they are not required to establish the diagnosis, nor are they considered useful to evaluate the effectiveness of dialysis. Dialysis and renal transplantation are generally effective treatments for partially reversing the neuropathy of ESRD, but EDX improvement is a late finding. Table 12 lists diseases that have EDX features of mixed sensory and motor conduction slowing and axonal loss.

<table>
<thead>
<tr>
<th>Table 12. Mixed sensory and motor, conduction slowing and axonal loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
</tr>
</tbody>
</table>

SUMMARY

In summary, patients with clinical features of neuropathy can be categorized into convenient classifications using NCSs. The groupings described in this manuscript separate neuropathies into those that are sensory, motor, or both, and into conditions which are predominately axonal loss or demyelinating (uniform or multifocal). In many patients, proper application of the principles outlined in this manuscript can direct the referring physician towards a specific and potentially treatable cause of the neuropathy.
REFERENCES

Basics With the Experts
CME Questions:

1. When evaluating for lumbosacral radiculopathy, all the following are important, except:
   A. Needle EMG of six muscles including the paraspinals.
   B. Sensory nerve conduction in the affected limb.
   C. Peroneal F-wave latency.
   D. Motor nerve conduction in the affected limb.

2. All the statements regarding the needle EMG evaluation are true, except for which one?
   A. Needle EMG should be avoided if a patient is anticoagulated.
   B. It is important to perform in most cases.
   C. There are minimal if any risks with such testing.
   D. Skin preparation with alcohol is unnecessary.

3. In order to accurately identify a lumbosacral radiculopathy that can be confirmed by needle EMG, how many muscles, one of which being the paraspinal muscles, must be studied?
   A. Four.
   B. Six.
   C. Eight.
   D. Ten.

4. Which of the following statements are true regarding radiculopathies?
   A. The F-wave latencies are an excellent screening test for subtle radiculopathies.
   B. The sensory responses in the affected limb should be of normal amplitude.
   C. Needle EMG has a very high sensitivity (> 95%) for such disorders.
   D. Paraspinal muscle recruitment and degree of polyphasicity should be used to identify radiculopathy, even in the absence of other findings.

5. Which of the following statements is true regarding radiculopathies?
   A. There is no relationship between symptom duration and the probability of fibrillations in any proximal or distal muscle.
   B. Lumbar paraspinal muscle examination with needle EMG results in a high rate of false positive findings.
   C. Reduced CMAP in involved muscles is commonly seen in radiculopathies.
   D. Lumbar MRI findings demonstrate few false positive disk bulges or disk herniations.

6. The Combined Sensory (Robinson’s) Index used for carpal tunnel syndrome:
   A. Is a sensitive test for median neuropathy at the wrist.
   B. Can be used to differentiate median from ulnar neuropathy.
   C. Is difficult to use in most cases.
   D. Is most helpful when differentiating radiculopathy from median neuropathy.
   E. Uses the addition of sensory amplitudes for the median antidromic and mid-palmar study.

7. The most common site for ulnar neuropathy is:
   A. In the hand.
   B. In Guyon’s canal.
   C. In the cubital tunnel.
   D. At the lacertus fibrosis.
   E. In the axilla.

8. The best test to define ulnar neuropathy at the elbow is:
   A. The ulnar antidromic digit V study.
   B. Median-ulnar antidromic digit IV study.
   C. Dorsal ulnar cutaneous study.
   D. Ulnar motor segmental stimulation.
   E. Side to side ulnar motor comparison.
9. Carpal tunnel syndrome includes all of the following except:
   A. Paresthesias in the fingers and/or hand.
   B. Night pain.
   C. Positive “flick” sign.
   D. Pronation weakness.
   E. Thenar atrophy.

10. To differentiate median neuropathy at the wrist from a more proximal median neuropathy, the best muscle to test on needle examination is:
   A. Flexor pollicis longus.
   B. Pronator teres.
   C. Flexor digitorum profundus.
   D. Flexor sublimis.
   E. Flexor digiti minimi.

11. During needle electrode examination in a muscle, a single motor unit potential fires at a maximum of 6 Hz. No other motor unit action potentials are observed. Which statement is most accurate?
   A. Recruitment is reduced.
   B. Recruitment is early.
   C. Activation is reduced.
   D. Recruitment ratio is 2.
   E. Interference pattern is full.

12. In a young man with hypercarbia, myotonic discharges are observed on needle electrode examination of the cervical paraspinal muscles. Which disease is most likely?
   A. Multifocal motor neuropathy.
   B. Adult onset Pompe disease.
   C. Myophosphorylase deficiency.
   D. Brainstem glioma.
   E. Lambert-Eaton myasthenic syndrome.

13. A woman undergoing EDX assessment for hip girdle weakness has low amplitude median and ulnar CMAPs with normal median and ulnar sensory NCS. What should be the most appropriate next step in her EDX evaluation?
   A. Needle electrode examination in intrinsic hand muscles.
   B. Needle electrode examination in C8/T1 paraspinal muscles.
   C. Simultaneous, 2-channel recording for Martin-Gruber anastomosis.
   D. Musculocutaneous motor NCS.
   E. Median and ulnar CMAPs immediately after 10 seconds maximal voluntary contraction.

14. Needle electrode examination in a weak muscle reveals polyphasic motor unit potentials with increased duration. Audio analysis of a single such motor unit potential reveals no change in pitch on repeated firing. What type of process is most likely?
   A. Primary neuromuscular junction disorder.
   B. Myopathy.
   C. Early reinnervation.
   D. Acute denervation.
   E. Suprasegmental process (e.g. corticospinal or extrapyramidal disorder).

15. Approximately what percentage of patients who have had diabetes for 25 years will be found to have a polyneuropathy?
   A. 10%.
   B. 20%.
   C. 35%.
   D. 50%.

16. Which is the following is the most common connective tissue disorder that gives rise to a polyneuropathy?
   A. Sjogren’s syndrome.
   B. Polyarteritis nodosum.
   C. Wegener’s granulomatosis.
   D. Rheumatoid arthritis.

17. Mee’s lines are observed in which of the following toxic neuropathies?
   A. Lead.
   B. Arsenic.
   C. Mercury.
   D. N-hexane.

18. In an investigation for the cause of a paraproteinemia in a patient with a polyneuropathy, the most likely etiology will be?
   A. Amyloidosis.
   B. Monoclonal gammopathy of undetermined significance (MGUS).
   C. Osteosclerotic myeloma.
   D. Multiple myeloma.

19. Which of the following treatments would be considered standard of care for a patient with acute inflammatory demyelinating polyneuropathy (AIDP):
   A. Intravenous immunoglobulin.
   B. Azathioprine.
   C. Corticosteroids.
   D. Alpha interferon.