Neuromuscular Update I

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2008 Neuromuscular Update Course C
AANEM 55th Annual Meeting
Providence, Rhode Island

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American Association of Neuromuscular & Electrodiagnostic Medicine
2621 Superior Drive NW
Rochester, MN  55901
Printed by Johnson Printing Company, Inc.
Authors had nothing to disclose.

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OBJECTIVES The overall objective of this two-part neuromuscular update course is to present participants with clinical cases in neuromuscular diseases. At the end of the entire course, participants will learn how to diagnose, evaluate, and in some instances treat neuromuscular diseases. This course is an excellent review of neuromuscular medicine. Update I covers oculobulbar weakness, acute flaccid weakness, floppy infant, and myeloneuropathy.

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

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

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CME for this activity is available 9/08 - 9/11.
CASE DESCRIPTION

History

A 36-year-old woman presented in August of 1999 with a 10-month history of nasal dysarthria that worsened toward the end of the day. She later developed horizontal diplopia that would first appear 20 minutes after awakening and fluctuate during the course of the day. Over this 10-month period, she also noticed neck weakness. The patient would have to strain to keep her head upright since it would tend to fall forward. There was mild dyspnea, dysphagia with nasal regurgitation beginning 7 months prior to her visit, occasional ptosis, and arm weakness that was greater than leg weakness. She had some difficulty walking for approximately 5 months. The patient denied sensory symptoms.

Past medical history was otherwise unremarkable. There was no family history of disorders causing weakness.

Before proceeding with the examination, are there any medications/supplements that the physician should ask the patient whether or not they are taking?

Examination

Mental status was normal. On cranial nerve examination, there was mild right ptosis, but extraocular motility was intact. There was clear fatigable eyelid weakness on sustained upgaze. Facial weakness was moderate on eye closure and mild in the lower facial musculature. Tongue strength was 4+ without atrophy or fasciculations. Neck flexion and extension were both graded 4-. Proximal arm and leg muscles were 4+ with milder weakness of distal upper limb groups including the intrinsic hand muscles. However, distal lower limbs were normal. No limb fasciculations were seen. Tendon reflexes were normal throughout. Sensation to all modalities was intact. Coordination and gait testing was normal.

Prior Studies

Acetylcholine receptor (AChR) binding antibodies were negative. Other pertinent laboratory results included negative antinuclear antibodies (ANA) and normal thyroid stimulating hormone (TSH). Chest computed tomography 2 months prior to her clinic visit showed no abnormalities.

Current Studies

AChR binding, modulating, and blocking, as well as striated muscle antibodies, returned negative. Voltage-gated calcium channel (VGCC), anti-Hu, and anti-Ri antibodies were negative. Creatine kinase (CK) was normal at 42, and a repeat TSH was normal at 1.27. A 3 Hz repetitive nerve stimulation (RNS) recording from the abductor digiti minimi (ADM) with a baseline amplitude 13.8 mv showed a 17% decrement at baseline that increased up to 20% 6 minutes after prolonged exercise. Repair of the decrement to 3% was seen immediately following brief exercise. Similar decremental patterns were seen on 3 Hz RNS of the orbicularis oculi, peaking at 20% 4 minutes after exercise, and of the trapezius, peaking at 15% at both 4 and 6 minutes following exercise.

What should be the physician’s next study or should the physician be satisfied with the work-up of the patient at this point?
DIFFERENTIAL DIAGNOSIS

Myasthenia Gravis

Myasthenia gravis (MG) is not uncommon as it has a prevalence as high as 2 to 7 cases per 10,000 population. Overall, there is a slight female predominance of 3:2, although males predominate in older age groups, and in some clinics, there are more reports of male MG patients than of female patients. The disease onset can occur at any age, but peaks are observed in the 3rd and 6th decade. MG is characterized by weakness and fatigability with typical involvement of the ocular, bulbar, truncal, and extremity skeletal muscle. The ocular manifestations are ptosis and diplopia, whereas the bulbar manifestations are dysarthria, dysphagia, and dyspnea. Proximal limb muscles tend to be weaker than distal ones. While classically there is worsening of symptoms with fatigue, stress, or during later hours of the day, temporal symptoms are not always elicited.

In this study, the patient had been previously diagnosed with MG based on presentation and abnormal RNS. Fatigable weakness in the eyelid, bulbar, neck, and limbs is all consistent with the diagnosis. Although a complete panel of AChR antibodies was negative, 15% of generalized MG patients will not harbor these antibodies. As was will see, even equivocal responses to anticholinesterase therapy, intravenous immunoglobulin (IVIg), and thymectomy do not rule out the diagnosis. Single-fiber electromyography (EMG) was not performed on this patient, but from a diagnostic standpoint, the contribution would have been minimal.

Another test to consider is anti-muscle specific tyrosine kinase (MuSK) antibodies. One form of MuSK MG has prominent facio-pharyngeal involvement, and these patients are often more refractory to conventional therapies. The response to cholinesterase inhibitors is variable in MuSK MG patients; many become worse or have profuse fasciculations with these medications. Pyridostigmine and IVIg in particular have not been helpful in treating a majority of these patients. The efficacy of thymectomy remains poorly defined in MuSK MG. Studies have shown no or minimal thymic abnormalities in these patients, in contrast to AChR-Ab positive MG. On the other hand, the favorable response to plasma exchange and an ultimately good outcome are typical for MuSK MG. In several series, approximately 75% of MuSK MG patients eventually achieved remission or were in minimal manifestation status. Table 1 summarizes the immunomodulatory therapies for MG.

Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome (LEMS) usually begins gradually and is characterized by fatigability and weakness in a limb-girdle distribution. Unlike MG, patients may note that the weakness is worse soon after awakening, but will improve later in the day. While exercise can transiently improve strength, persistent exertion causes fatigue. Cranial nerve and respiratory involvement is less common than in MG. Up to 50% of patients can have mild degrees of ptosis, diplopia, dysphagia, and dysarthria. Patients may also experience autonomic involvement including dry mouth and eyes, impotence, blurred vision, and orthostasis. On examination, there is a limb-girdle pattern of weakness and reduced or absent deep tendon reflexes. A malignancy is present in approximately 50% of adult LEMS patients. The tumor is usually a small cell carcinoma of the lung, but other malignancies such as renal cell carcinoma and hematologic tumors occur. Malignancy is more common in men than in women, and is more likely to occur in those who are chronic smokers or over age 50.

LEMS would seem an unlikely diagnosis in this case. The history reveals no autonomic involvement and reflexes were normal on examination. With low rate repetitive stimulation, LEMS patients typically show a decremental response (Figure 1), but immediately after exercise, there is prominent facilitation, something not observed in this case. Low-amplitude motor responses are typical for LEMS, another feature missing from this case. Finally, VGCC antibody testing was negative.

Upon confirmation of a diagnosis of LEMS, an extensive search for an underlying malignancy is imperative. This should begin with radiologic studies and may require bronchoscopy or positron emission tomography (PET) scan. Initial treatment should be directed against the malignancy, as this may improve neurologic manifestations. Clinical experience suggests that immunotherapy without directed treatment of the underlying cancer produces little clinical benefit. When no malignancy is found, a repeat screening every 6 to 12 months is advised during at least the first 2 years of disease, or even longer in patients at risk for malignancy. In general, a trial of pyridostigmine is the first pharmacologic intervention, although it is often of limited benefit. Drugs that enhance the presynaptic release of ACh vesicles are most effective. Guanidine hydrochloride is the oldest drug in this group and has...
<table>
<thead>
<tr>
<th><strong>Agent</strong></th>
<th><strong>Initial dose</strong></th>
<th><strong>Maintenance dose</strong></th>
<th><strong>Onset of Action</strong></th>
<th><strong>Major Adverse Events</strong></th>
<th><strong>Lab Monitoring</strong></th>
<th><strong>Comments</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>15-20 mg qd, increasing by 5 to 10 mg q2-3 days; may begin with 60 mg qd and taper after benefit established</td>
<td>1.5 mg/kg a day, followed by slow alternate day taper (taper by 5-10 mg a month)</td>
<td>2-4 weeks</td>
<td>HTN, diabetes, weight gain, bone loss, cataracts, GI ulcers, psychologic disorders</td>
<td>K+, glucose every few months; bone density monitoring</td>
<td>Administer in single am dose; watch for early worsening in first week of administration and during the tapering phase</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>50 mg qd</td>
<td>Increase by 50 mg increments q 2-4 weeks to target of 2-3 mg/kg</td>
<td>2-10 months for initial responseUp to 24 months for peak</td>
<td>Fever, abdominal pain, n/v, anorexia, leukopenia, hepatotoxic, skin rash</td>
<td>CBC, LFTs 2-4 times in first month, then monthly</td>
<td>10% of patients cannot tolerate because of flu-like reaction; major drug interaction with allopurinol</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>100 mg bid</td>
<td>Increase slowly as needed to 3-6 mg/kg on bid schedule</td>
<td>1-3 months</td>
<td>Hirsuitism, tremor, gum hyperplasia, HTN, hepatotoxic, nephrotoxic</td>
<td>CBC, LFTs, BUN/Cr monthly. Follow trough drug levels Bioequivalence differs between preparations; avoid brand switching when possible</td>
<td>Diarrhea may resolve by switch to tid dosing</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>500-1000 mg bid</td>
<td>1000 to 1500 mg po bid</td>
<td>2-12 months</td>
<td>Diarrhea, vomiting, leukopenia</td>
<td>CBC weekly for 4 weeks, q2 weeks for 4 weeks, then monthly</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>3-5 mg/kg a day; can be preceded by intravenous pulse</td>
<td>2-3 mg/kg a day</td>
<td>2-6 months</td>
<td>Alopecia, leukopenia, nausea and vomiting, skin discoloration, anorexia hemmorh-agic cystitis, malignancy</td>
<td>CBC, chemistry panel, urinalysis every 2-4 weeks</td>
<td>Intravenous pulse therapy may be less toxic</td>
</tr>
<tr>
<td>Tacrolimus/ FK-506</td>
<td>3 mg a day</td>
<td>Increase up to 5 mg a day</td>
<td>1-3 months</td>
<td>Hypergly cemia, hypertension, headache, hyperkalemia, nephrotoxicity, diarrhea, nausea and vomiting</td>
<td>BUN/Cr, glucose, potassium, trough levels every few weeks initially, then less regularly</td>
<td>Insulin-dependent diabetes mellitus developed in 20% of post-renal transplant patients. Trough levels&lt;10 ng/ml have been effective in MG</td>
</tr>
<tr>
<td>Rituximab</td>
<td>375 mg/m2 weekly or every other week for 4 weeks</td>
<td>Can follow without further infusions or repeat 375 mg/ m2 dose every 8-12 weeks</td>
<td>1-3 months</td>
<td>Common: pruritis, nausea, vomiting, dizziness, headache. Uncommon: serious dermatologic events including Stevens-Johnson syndrome, aplastic or hemolytic anemia, leukopenia, thrombocytopenia, GI obstruction, tumor lysis syndrome (in lymphoma patients)</td>
<td>CBC, monitor hepatic function closely in viral hepatitis carriers</td>
<td>B lymphocyte counts fall rapidly following infusions. Both AchR and MuSK Ab titers are reported to fall with treatment. Progressive multifocal leukoencephalopathy is rare but of concern with this agent</td>
</tr>
<tr>
<td>IVIg</td>
<td>2 gm/kg over 2-5 days</td>
<td>0.4-1 gm/kg every 4 weeks; can attempt to decrease frequency over time</td>
<td>1-2 weeks</td>
<td>Headache, aseptic meningitis, nephrotoxic, ischemic events, fluid overload</td>
<td>BUN/Cr</td>
<td>Avoid in patients with recent ischemia</td>
</tr>
</tbody>
</table>

**bid** = two times a day; **BUN/Cr** = blood urea nitrogen to creatinine ratio; **CBC** = complete blood count; **bid** = twice a day; **GI** = gastrointestinal; **HTN** = hypertension; **IVIg** = intravenous immunoglobulin; **K+** = potassium; **LFTs** = liver function tests; **MG** = myasthenia gravis; **qd** = every day; **tid** = three times a day.
Mitochondrial Myopathy

Mitochondrial myopathy is a complex group of disorders resulting from mitochondrial dysfunction. Mitochondrial disorders include defects proximal or within the respiratory chain. Molecular defects can either involve mitochondrial deoxyribonucleic acid (mtDNA) or nuclear deoxyribonucleic acid (nDNA). Of note, most components of the electron transport chain are encoded by nDNA. It is also becoming clear that some nDNA mutations impair the replication and expression of mitochondrial genes; that is, they produce disease through disruptive intergenomic communication. The peculiar properties of mitochondrial genetics augment the complexity of phenotypic expression, as the degree of heteroplasmacy of mtDNA mutations can differ between tissues. Furthermore, some tissues are more susceptible to mitochondrial dysfunction than others. Major mitochondrial syndromes are summarized in Table 2. In general, mitochondrial myopathies are slowly progressive with limb-girdle weakness and exercise intolerance. Short stature, ocular involvement, and hearing loss are common features. Serum or cerebrospinal fluid lactate levels may be elevated at rest or after exertion. In many mitochondrial myopathies, muscle fibers contain increased numbers of structurally and functionally abnormal mitochondria. These accumulations produce the "ragged-red" appearance on trichrome-stained sections. Other morphologic abnormalities include reduced staining on cytochrome-c oxidase and succinate dehydrogenase preparations. For definitive diagnosis, genetic analysis is available commercially for some of the mtDNA disorders, including Kearns-Sayre syndrome, progressive external ophthalmoplegia, myoclonic epilepsy and ragged red fibers, and mitochondrial encephalomyopathy with lactic acidosis and stroke like episodes. Although the patient's oculobulbar presentation is not atypical for a mitochondrial disorder, family history negated a maternal inheritance pattern one would suspect in a mtDNA disorder. The degree of symptom and sign fluctuation and the decremental patterns on RNS would also argue against a mitochondrial myopathy.

Treatment of mitochondrial disorders includes the management of cardiac complications and anticonvulsant therapy for patients with seizures. Many clinicians recommend a battery of supplements and antioxidants including vitamins A, C, and E, coenzyme Q10, L-carnitine, and creatine. Exercise training may also play a role in management as it increases peak work, oxidative capacities, and functional performance.

Hereditary Inclusion Body Myositis

An autosomal dominant form of hereditary inclusion body myositis (h-IBM type 3; OMIM 605637) associated with myosin heavy chain IIa (MyHC IIa) gene mutations is characterized clinically by mild to severe proximal weakness and external ophthalmoplegia. Extraocular weakness typically begins with an upgaze paresis and progresses to involve other eye movements. Quadriceps may be severely affected with atrophy and weakness. Congenital joint contractures are present but tend to improve over time. Serum CK levels may be normal in children, and are mildly to moderately elevated (up to 10x normal) in adults. Myopathic features are present on EMG. Histopathologic findings on muscle biopsy demonstrate hypotrophic or absent type 2A fibers, non-specific myopathic features including marked variability of fiber size and central nuclei, and disorganization of the intermyofilamentous network in type 2A fibers. Rimmed vacuoles are present in more severely affected biopsies with neighboring tubulofilamentous inclusions of 15 to 20 nm diameter. As with other forms of h-IBM, there is no definitive therapy for h-IBM type 3.

The absence of early childhood involvement, positive family history and fixed extracocular motility deficits as well as the presence of decremental patterns on RNS would argue against an h-IBM diagnosis.

Oculopharyngeal Muscular Dystrophy

Oculopharyngeal muscular dystrophy (OPMD) is a late (usually after 5th decade) adult-onset disease characterized by ptosis, dysphagia, external ophthalmoplegia, and mild proximal limb weakness. In North America, French Canadians in Quebec and Spanish-American families in New Mexico, Colorado, and Arizona are the most commonly affected ethnic groups. On muscle biopsy, rimmed vacuoles are seen on light microscopy and unique nuclear filament inclusions of 8.5 nm diameter on electron microscopy. Autosomal dominant and recessive forms are recognized, with both inheritance patterns related to polyadenylate-binding protein nuclear 1 gene defects on 14q11. GGC trinucleotide repeat lengths greater than 6 are abnormal. Molecular testing is commercially available. Polyalanine tract expansions produced by the gene mutation accumulate into undegradable intranuclear inclusions that are believed to sequester other nuclear proteins and interfere with cellular processes.
This patient did not have fixed ophthalmoplegia or ptosis. Also, limb weakness progressed more quickly than is expected for OPMD. There was no supportive family history, and the decrements on RNS would not be typical for this diagnosis.

**Diagnostic Study**

In January 2004, MuSK antibodies were ordered and returned positive. By this point, the patient had achieved complete stable remission after several years of struggling with MG-related weakness and receiving a variety of interventions.

**Management**

Prior to the patient’s initial visit, she had been placed on pyridostigmine. There was no more than mild improvement at doses up to 60 mg 4 to 5 times per day. In June 1999, an outside neurologist placed her on prednisone, titrating up to 60 mg every other day. This also resulted in only mild improvement. In November 1999, she underwent extended transsternal thymectomy. Benign thymic tissue was found. There was no appreciable improvement over the ensuing months. Prior to the thymectomy, she received preoperative plasma exchange (two plasma volume exchanges). She noted marked improvement from this intervention. Following her thymectomy, she underwent several more plasma exchanges through July 2001. Over a 5-month interval during this 2-year period following her initial visit, she received IVIg, 2 gm/kg induction followed by 0.4 gm/kg month. There was mild improvement with IVIg, but her response to plasma exchange was considerably greater. In June 2000, she was placed on azathioprine, titrated up to 200 mg a day. Over time, she felt that this intervention had the greatest impact on some of her symptoms, especially the diplopia. By January 2003, she had been weaned off of all medications, including corticosteroids, pyridostigmine, and the azathioprine. She was classified as being in remission at that point, and remained in complete stable remission on follow-up through 2006, at which point she relocated from North Texas.

**Case Discussion**

Although this patient had clinical and electrodiagnostic features typical of MG, in some MuSK MG patients, weakness is limited to one or more anatomic regions, frequently with marked atrophy, especially of facial or oropharyngeal muscles. In the author’s clinic, MuSK MG patients are more likely than their MuSK-negative cohorts to present with respiratory symptoms or neck extension weakness. Scoliosis and adynamia of the upper esophagus has been seen as a manifestation of focal weakness in MuSK MG. (Sanders DB, Juel VC. MuSK-antibody positive myasthenia gravis: Questions from the clinic. J Neuroimmunol 2008; In Press). Most MuSK MG patients have more than just ocular muscle weakness, but weakness limited to ocular muscles have been reported.1
A markedly greater female predominance has been consistently reported among MuSK MG patients than in MuSK negative MG. There is also a marked racial predominance in the author’s clinic, and it has been found that a woman with AChR antibody-negative MG is twice as likely to have MuSK MG if she is African-American. The distance north of the equator also appears to be a major determinant of the proportion of patients with MuSK MG. Within the European and American populations, high proportions (up to 40%) are found around latitude 40 degrees north, but further north, the proportion falls steeply with lower values in northern Europe. Conversely, among Pacific countries, the proportion increases from 2% at 15 degrees north of the equator to around 35% at 37 degrees north. This suggests that an environmental factor plays a role in the etiology of MuSK MG.

RNS and jitter studies are usually more abnormal in the face than the limbs, but may give diagnostic findings only if symptomatic muscles are tested. In this study, the MuSK MG patients jitter was abnormal in the extensor digitorum in only 50%, as compared to 80% of AChR negative, and 91% of AChR-positive patients.

In many MuSK MG patients, EMG studies demonstrate short duration, complex, excessively recruited motor unit action potentials (MUAPs), suggesting a myopathy. Quantitative measurements in facial muscles have demonstrated reduced MUAP duration and findings on turns-amplitude analysis similar to a myopathic control group, suggesting that the atrophy is not neurogenic but is akin to a myopathic process.

MuSK MG patients frequently do not improve with cholinesterase inhibitors, which actually worsen weakness in some, and may produce profuse fasciculations. Repetitive discharges after the compound motor action potential may be seen in these patients after even low doses of these medications. These findings indicate an abnormal sensitivity to ACh and may be a useful indicator of the adverse effects of these medications. The cause of this sensitivity to ACh is unknown, but may be related to an abnormality of acetylcholinesterase function.

Almost all MuSK MG patients improve with corticosteroids or plasma exchange, and the latter frequently produces rapid and dramatic improvement. Most patients also respond to other immunomodulatory therapy; the response to other treatments is less predictable. Overall, 90% of our MuSK MG patients have improved with selected treatment with 50% having reached a Myasthenia Gravis Foundation of America Post-Intervention Status of remission or minimal manifestations. As with this patient, two other patients at the author's institution are in complete stable remission following surgical removal of what appeared to be a normal thymus. Thymus histology is normal in most MuSK MG patients, arguing against an intrathymic disease pathogenesis. However, the high incidence of improvement, even complete stable remission, that has been seen following thymectomy suggests that removal of the thymus may be of benefit in MuSK MG. Without controlled, prospective studies, benefit from thymectomy cannot be determined, nor can it be excluded.

REFERENCES

Acute Flaccid Weakness

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CASE DESCRIPTION

History

In August 2003, a 36-year-old previously healthy woman from Michigan developed a “flu-like” illness consisting of diarrhea, vomiting, and abdominal pain. Four days later, she suddenly noted rapidly progressive leg weakness and became unable to walk in less than 2 hours. A few hours after she noted leg weakness, her left arm became weak and within 12 hours it was flaccid. She reported no sensory abnormalities. She had mild low back pain. She had one episode of bowel incontinence, but believes that was due to severe diarrhea. She reported a mild persistent headache. She reported a mild persistent headache. She had no known toxic exposures, but did recently return from her family’s yearly July 4th camping trip. No other family members were ill. In the emergency room, she was initially fully alert, but 12 hours after admission was noted to be confused.

Examination

On initial examination in the emergency department, the patient had a low grade fever of 38.5°C. She was slightly lethargic but fully oriented without neck stiffness. Cranial nerve examination was normal with the exception of mild bifacial weakness including slight weakness of both lip and eyelid closure. The limbs were asymmetrically weak, with Medical Research Council (MRC) grade 4 power in most right arm muscles, MRC grade 0 power in most left arm muscles, and MRC grade 3 power in most muscles of the left leg, while the right was only mildly weak. The sensory examination was normal. Reflexes were normal in the right arm, absent in the left arm, and trace in the legs. She could not stand or walk. Anal sphincter tone was normal.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute flaccid paralysis is large and includes a few common “horses” such as Guillain-Barré syndrome (GBS) and a large number of rare causes or “zebras” (Table 1). Most neuromuscular clinicians will make a diagnosis of acute inflammatory demyelinating polyneuropathy (AIDP) many times in their career, but the clinician must also remain poised to recognize a single case of buckthorn intoxication (or other rare cause) which is unlikely to present more than once in a clinician’s lifetime. It is not appropriate or practical to screen for every rare cause in every case. Careful attention to the details of the patient history and examination often provides clues that a “zebra” may be afoot.

In the above case, one of the most striking clinical features is the extremely rapid progression of weakness. Other important features include the marked asymmetric arm weakness, lack of sensory complaints, antecedent/concurrent illness, and reflexes which remain present despite prominent weakness. These features should alert the clinician that this may not be a typical case of GBS and lead to a widened search for alternative diagnoses.

The marked asymmetry and rapid progression should lead the examining physician to consider cerebrovascular disease. The complete loss of reflexes on the left side, lack of facial involvement, and slight involvement of the right arm are a bit unusual, but do not alone exclude this possibility.

The patient’s age is another reason to consider demyelinating disease. The progression over hours is a bit unusual, but both inflammatory lesions of the brain and/or spinal cord remain possibilities.
Acute Flaccid Weakness

Although extremely rapid progression is not typical of GBS, a number of other disorders should be considered. Diseases with particularly rapid progressive weakness include paralytic poliomyelitis or infection with other neurotropic viruses, various toxins including biologic agents such as botulism, metabolic disorders such as periodic paralysis, and acute myelopathy such as transverse myelitis. A number of the listed disorders are infectious and would fit well with the patient’s concurrent illness.

The patient’s lack of sensory complaints and lack of abnormalities on the sensory examination provide powerful localizing information. The differential diagnosis now is reduced to include only disorders confined to the motor unit (MU), that is, the anterior horn cell, motor nerve, neuromuscular junction, and muscle. AIDP typically has sensory involvement, but one subtype of GBS, acute motor axonal neuropathy, spares sensory function. Most lesions of the spinal cord would cause both sensory and motor dysfunction, making myelitis much less likely.

The asymmetric weakness in this patient is another feature which may help limit the differential diagnosis. Asymmetric weakness is typical with poliomyelitis due to the polio virus itself, or to other enteroviruses. Infection with other flaviviruses, such as West Nile virus, also causes asymmetric weakness.

**EVALUATION**

Additional testing beyond the history and physical examination often allows a precise diagnosis to be made in cases of acute flaccid paralysis. Electrodiagnostic (EDX) testing is the mainstay of the evaluation of acute flaccid paralysis, yet it should be noted that nerve conduction studies (NCSs) and electromyography (EMG) serve as an extension of the physical examination, and rarely provide a precise diagnosis. Further, EDX testing may be relatively insensitive in the acute period. Unless there was distal conduction block or neuromuscular junction abnormalities, NCSs would not be helpful in the first day or two. If there was denervation from motor neuron or proximal nerve lesions, conduction studies could not distinguish Wallerian degeneration from conduction block for at least 4 days. Because of the severity of symptoms and the acute nature of the presentation, early diagnosis will remain dependent on other testing.

Despite these limitations, EDX testing may be very useful after 4 to 5 days to provide accurate localization of the lesion affecting the MU as well as provide very specific information which markedly narrows the differential. For example, the identification of signs of demyelination brings the diagnosis of AIDP to the forefront and prominently restricts the differential diagnosis. In addition, EDX testing may confirm the lack of sensory involvement and highlight asymmetry. With this data available, specific additional testing can be obtained.

Magnetic resonance imaging (MRI) of the brain and spinal cord should determine if a central nervous system disorder (e.g., ischemic, hemorrhagic, infectious, or an inflammatory disorder) is present. In addition, a lumbar puncture to evaluate for abnormalities in the cerebrospinal fluid (CSF) is indicated. An elevated CSF protein level without pleocytosis (i.e., albuminocytologic dissociation) is typical of AIDP, but may be seen in many other disorders. The lumbar puncture results may be even more revealing when a CSF pleocytosis is present. Although such a pleocytosis can occur in GBS, it is atypical and should trigger a search for an alternative diagnosis. Human immunodeficiency virus (HIV), cytomegalovirus, and West Nile virus infection are among the most common causes of flaccid paralysis in which a CSF pleocytosis is present.

Serologic testing should be guided by the remaining disorders on the differential diagnosis. Metabolic disturbances such as hypophosphatemia, hypermagnesemia, and hypokalemia are easily excluded on most initial hospital chemistry panel screens. Abnormalities in liver function can occur with many intoxications, some infections, and porphyria. The combination of

<table>
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<tr>
<th>Differential diagnosis of acute flaccid paralysis</th>
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<tr>
<td><strong>Relatively common causes, or those which are critical to identify immediately due to the importance of early treatment</strong></td>
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<td>Guillain Barré syndrome</td>
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<td>Vasculitic neuropathy</td>
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<tr>
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<tr>
<td>Myasthenia gravis</td>
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<tr>
<td>Hypophosphatemia</td>
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<td>Polio-like infections (West Nile virus, Enteroviruses, Herpesviridae, CMV, EBV)</td>
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<td><strong>Rare causes of acute flaccid paralysis</strong></td>
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<td>Botulism</td>
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<td>Heavy metal intoxication (arsenic, gold, thallium)</td>
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<td>Chemical toxins (organophosphates, vacor)</td>
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<td>Biologic intoxication (buckthorn, marine toxins, snake bite, tick paralysis)</td>
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<td>Periodic paralysis</td>
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<td>Rhabdomyolysis/metabolic myopathy</td>
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<tr>
<td>Polymyositis</td>
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<td>Paraneoplastic disorders</td>
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| Polymyositis |
| Paraneoplastic disorders |

CMV= Cytomegalovirus , EBV= Epstein-Barr virus, HIV= human immunodeficiency virus
abnormal liver function studies and pancytopenia should trigger an investigation of arsenic intoxication. Confirmation is obtained by measurement of hair or nail arsenic levels or by 24-hour urinary arsenic excretion measurement. Elevation of white blood cell (WBC) count suggests an antecedent or concurrent infection. Measurement of antibody titers to specific infectious agents may lead to a definite diagnosis.

Results

An MRI of the brain and cervical spine performed in the first 24 hours was normal. There was an elevated serum WBC count of 15 (10^3/mm^3). Routine chemistry battery was normal.

Lumbar puncture revealed a CSF protein of 125 mg/dl with a predominantly lymphocytic pleocytosis (88 WBC, 10^3/mm^3). Rapid immunologic testing for herpes simplex virus and bacterial meningitis was negative. Serum and CSF Lyme titers were negative. HIV testing was negative. The CSF venereal disease research laboratory results were negative.

NCSs and EMG were performed on day five of admission. All sensory responses in the arms and legs were normal. The motor responses were absent in the left leg and left arm. The right arm and leg had relatively normal responses. The amplitudes did not increase following 15 seconds of exercise (brief exercise test). No decrement was noted on 2 Hz repetitive stimulation of the facial nerve. Needle EMG examination revealed no abnormal spontaneous activity. It should be noted that the study was performed a few days after onset of weakness and thus, positive waves and fibrillation potentials would not be expected to be present. MU morphology was normal, with no voluntary units in the left arm and leg.

Assessment

In this case, the rapidly progressive asymmetric weakness, the CSF pleocytosis, the viral prodrome, and the development of mild confusion are features supportive of a polio-like illness producing acute flaccid weakness. Polio virus itself is no longer an important cause of weakness in the developed world. Vaccine associated poliomyelitis is a persistent but exceedingly rare event, occurring in approximately one case per 2.5 million oral polio vaccine doses. Non-polio enteroviruses and other neurotropic viruses prove to be more common causes of acute flaccid paralysis. Serologic testing for enteroviruses (Coxsackie A and B, echovirus, enterovirus 70 and 71), HIV, Herpesviridae (cytomegalovirus, Epstein-Barr virus, herpes simplex 1 and 2, varicella zoster) and West Nile virus should be considered in cases such as the one presented. In this patient, both CSF and serum testing revealed the presence of IgM antibodies to West Nile virus. This allows for a diagnosis of probable West Nile virus infection. Confirmation requires sophisticated testing such as the plaque reduction neutralization test performed by the Centers for Disease Control and Prevention. IgM enzyme-linked immunosorbent assay testing is available in or through most hospital laboratories in the United States.

DISCUSSION

West Nile virus, a member of the family flavivirus, was first isolated in 1937 in Africa. It was first identified in the United States in New York City in 1999, and the number of identified cases increased rapidly in the following few years (Figure 1). The virus is transmitted via the Culex pipiens mosquito, with birds being the primary reservoir of infection. Cases have now been identified in every state in the continental United States. Of infected individuals, only about one in 200 develops neurologic disease. Approximately 50% of those develop clinically important weakness. A population-based study during a West Nile virus epidemic in Colorado identified an overall incidence of West Nile virus associated paralysis of 4.3/100,000. In most cases, signs of systemic viremia, and often meningoencephalitis, accompany the onset of weakness. However, acute flaccid paralysis can occur in patients without other overt signs of West Nile infection. Such cases pose a significant diagnostic challenge. At least two distinct

![Figure 1](westnile.png)
weakness syndromes have been reported in patients infected with West Nile virus.\textsuperscript{1,3,5,6} The most common cause of weakness is likely the primary loss of anterior horn cells with sparing of sensory function. That is the apparent mechanism in the presented case. Less commonly, AIDP has been reported in conjunction with West Nile infection.

Treatment of flaccid weakness related to West Nile virus infection largely consists of supportive care, unless features of typical AIDP are identified. In the latter scenario, treatment with intravenous immunoglobulin 400mg/kg/day for 5 days or a course of plasma exchange is likely as effective as these interventions are in routine cases of AIDP. No known treatment exists for the acute anterior horn cell loss most typical of flaccid weakness in West Nile virus infection.\textsuperscript{9} In cases where the degree of denervation is of mild or moderate severity, considerable recovery is possible. However, if the denervation is severe, the prognosis for recovery of functional strength is likely very poor.

\textbf{REFERENCES}

A 6-month-old male infant is referred for evaluation of severe hypotonia and failure to achieve motor milestones. The baby was the product of a term gestation, born to a Gravida 3, Para 3, 29-year-old mother. In retrospect, the mother believes that third trimester fetal movements were not as vigorous as those noted in her two previous pregnancies. The baby presented vertex and was delivered vaginally. Birth weight was 2700 grams. APGAR scores were 8 at 1 and 5 minutes with points off for color and tone. However, the child was not noted to be an unduly “floppy baby” and the baby fed well.

Initial concerns occurred at 4 months of age when the child failed to achieve milestones that included rolling over and reaching for objects. The maternal grandmother noted that the baby’s head control was worse than it had been in the newborn period. All caretakers were concerned that the baby exhibited little spontaneous movement of arms or legs. However, they were encouraged by the baby’s beaming smile and bright eyes “which followed our every movement as we circled his crib.”

There is no family history of parental consanguinity or neuromuscular (NM) disease. Physical examination reveals an alert hypervigilant child who makes ready eye contact and smiles socially at the examiner. The baby’s respiratory pattern is unusual with retraction of the chest wall and upward heaving of the abdomen with each inspiration. There is a generalized decrease in muscle mass but no joint contractures. There is no visceromegaly. The baby lies in bed with almost no spontaneous limb movement. There is profound generalized hypotonia with almost no resistance to passive movement about all major joints. There is no reflex movement to gentle noxious stimuli delivered over the sternum and soles of his feet. He responds to this indignity with a weak cry. His arms are held in abduction with flexion at the elbows and pronation of the forearms. His legs are held in extreme abduction with flexion at the knees and ankles. Head control is essentially absent with the baby held prone and there is severe head lag when the child is passively pulled to a seated position from a supine position. With ventral suspension under the axillae, the baby slips through the examiner’s hands. The child is globally areflexic. There is a behavioral response to tickle and pinprick administered over the trunk and limbs, but no active withdrawal from noxious stimuli. Upon gently opening the baby’s mouth, fine, nearly constant flickering tongue movements (“fasciculations”) are seen.

Screening laboratory studies include a normal complete blood count and basic metabolic panel. His creatine kinase (CK) is elevated at 300 IU (normal < 170 IU).

DISCUSSION

Weakness that is associated with either failure to achieve motor milestones or loss of previously acquired motor function is the symptom most likely to result in urgent NM referral. The clinician’s first task is localization of the problem to the central or peripheral nervous system; specific syndromes mimicking NM diseases must also be excluded.

Weakness due to central nervous system (CNS) disorders is usually characterized by an “elective” distribution with maximal deficits in antigravity muscles, and preservation or exaggeration of deep tendon
reflexes. Infants and toddlers often demonstrate hypotonia which is disproportionate to the degree of weakness. Asymmetric motor deficits and concurrent difficulties with cognitive dysfunction, seizures, and other “hard” symptoms of CNS dysfunction point to a central disorder. Lower motor unit (MU) disorders usually demonstrate symmetric proximal or distal gradient. Low tone is proportional to weakness. Deep tendon reflexes are usually depressed or unobtainable (an important exception being post synaptic disorders of the NM junction). Several disorders that are traditionally classified as NM diseases may present with or be dominated by CNS symptoms. The cognitive impairment seen in children with the infantile form of myotonic dystrophy, Duchenne muscular dystrophy, and mitochondrial encephalomyopathies are a few examples.

Several infant onset NM diseases manifest clinical phenotypes that are so distinct and stereotyped that a diagnosis can be established on the basis of the history and physical examination. Most of these “spot diagnoses” are genetic disorders, and several may be confirmed by deoxyribonucleic acid (DNA) testing as the sole investigation. When an infant presents with a less specific clinical picture, a systematic consideration of disorders affecting each tier of the lower MU must be considered (Table 1). It is appreciated that most of the NM diseases listed have limited specific therapeutic interventions. Important exceptions include disorders of NM transmission and classic infant onset Pompe disease, which is treated with recombinant acid alpha glucosidase enzyme replacement therapy.8

**Spinal Muscular Atrophy**

The clinical data presented above paint a pathognomonic picture of a child with Type 1 spinal muscular atrophy (SMA). The constellation of paralytic hypotonia, paradoxical abdominal breathing, and tongue “fasciculations” place SMA on top of the list of differential diagnoses. The trivial elevation of CK is frequently found in children with acute or subacute neurogenic disorders.

Other lower MU disorders can present a clinical phenotype very similar to that described above (Table 1). However, the classic clinical picture presented in this case report justifies proceeding with DNA studies as the next diagnostic step. It is easy to make an initial diagnoses of SMA in children and then later find that the correct diagnosis is a congenital muscular dystrophy or congenital myopathy.

Proximal 5q SMA is part of a family of motor neuronopathies. SMA is the most common cause of paralytic infantile hypotonia and is the most common genetic lethal disorder in children under 2 years of age. The disease is inherited as an autosomal recessive trait. Gene frequency is estimated at 1:60 to 1:80. The incidence of childhood SMA has been estimated between 1:6000 and 1:15,000 live births. Symptoms of the disease are attributed to degeneration of anterior horn cells in the spinal cord and brainstem, culminating in flaccid weakness, respiratory insufficiency, and bulbar deficits. Because the clinical spectrum of proximal SMA is dramatic, the use of an arbitrary classification system based on age of onset of symptoms and maximal motor milestones achieved has been employed. By convention, four SMA phenotypes are defined.10,17

<table>
<thead>
<tr>
<th>Table 1 Neuromuscular diseases of the infant</th>
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<tbody>
<tr>
<td>(The more common of rare diseases)</td>
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<td>Motor Neuron</td>
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<td>Classic autosomal recessive proximal spinal muscular atrophy (SMA)</td>
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<td>SMA with respiratory distress</td>
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<td>Nemaline myopathy</td>
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<td>Congenital fiber-type disproportion</td>
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<td>Desmin storage myopathy</td>
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<tr>
<td>Metabolic muscle disorders (Pompe disease; Lipid storage myopathy)</td>
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<td>Mitochondrial myopathies (including SCO2 mutations and mitochondrial depletion syndrome)</td>
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<tr>
<td>Syndromic Hypotonia</td>
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<tr>
<td>Down syndrome</td>
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<td>Prader Willi syndrome</td>
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</table>

Type 1 SMA presents with clinical symptoms before 6 months of age. These children are never able to achieve independent sitting.

Type 2 SMA presents with symptoms before 18 months of age. These children eventually sit unsupported but never achieve independent ambulation.

Type 3 SMA presents after 18 months of age. Children achieve independent ambulation. The clinical phenotype is broader than that described for younger children with Type 1 and Type 2 SMA, prompting Kugelberg and Welander to describe the phenomenon of “juvenile SMA mimicking muscular dystrophy.”

Type 4 SMA is known as “adult SMA”. Some of these adult onset patients have SMA reflecting 5q mutations identical to those defined in patients with earlier onset SMA. Others have genetically distinct disorders affecting motor neurons (MNs).
It must be appreciated that although proximal 5q SMA is far and away the most common form of infantile, genetic MN disease, other diseases including SMA with respiratory distress (SMARD), X-linked SMA, and SMA due to mitochondrial dysfunction may all present with remarkably similar clinical phenotypes.

**TYPE 1 SMA**

Werdnig and Hoffman independently described Type 1 SMA in the 1890s. A full century elapsed before the genetic defect was localized to chromosome 5q11.2-13. This was followed by the identification of mutations in the survival motor neuron (SMN) gene. The complexity of gene arrangements in the 5q11-13 domain thwarted early efforts to delineate candidate genes. This domain is characterized by an inversion duplication with near mirror images of several genes. In 1995, the mystery was solved. Two copies of the SMN gene were identified: a telomeric SMN1 copy and a centromeric SMN2 copy. A homozygous deletion, or point mutation, in the SMN1 gene is found in the vast majority of patients with SMA. A nearly identical gene, the centromeric SMN2 gene, is present in all patients with proximal 5q SMA. The clinical severity of the phenotype is in part determined by the copy number of the SMN2 gene. SMN1 and SMN2 genes differ in a single nucleotide substitution. The SMN genes are comprised of eight exons. The single nucleotide change in the SMN2 gene results in splicing out exon 7 of the messenger RNA (mRNA). The delta 7 messenger RNA (mRNA) results in the translation of a truncated unstable protein. However, approximately 10% of the protein translated from the SMN2 mRNA is full length. Thus, there is a "partial rescue" effect of the SMN2 gene. The number of SMN2 copies provides a rough correlate as to the clinically predicted phenotype. Homozygous or compound mutations of the SMN1 gene are found in all patients with proximal 5q SMA. A fetal conceptus harboring no SMN2 gene copies is nonviable, culminating in spontaneous pre-implantation miscarriage. Infants with only one SMN2 copy number usually have a severe clinical phenotype with symptoms often noted at birth (e.g., profound weakness, joint contractures, and clinical and EDX evidence of sensory as well as motor neuropathy). Patients with two copies of the SMN2 gene constitute the majority of infants with classic SMA type 1 (Werdnig Hoffman disease). Three copies of the SMN2 gene provide more protection and are usually associated with the Type 2 SMA phenotype. Patients with four or more copies of SMN2 usually present a Type 3 SMA (Kugelberg Welander) phenotype. Current commercially available DNA testing includes SMN1 deletions, SMN1 point mutations, and SMN2 copy number. However, a prediction of the clinical phenotype cannot be made solely on the basis of a SMN2 copy number.

The pathogenesis of SMA is incompletely understood. Although SMN is expressed in all tissues, SMN1 (full length) protein deficiency disproportionately affects lower MNs. SMN1 protein is localized in both the nucleus and cytoplasm of MNs. The nuclear SMN is largely associated with structures called gems which have a role in pre-mRNA editing (splicing) and mRNA metabolism. SMN protein does not act in isolation but as part of a stable multi-protein complex ubiquitously expressed in the cytoplasm and nucleus of all eukaryotic cells. In addition to SMN, the complex consists of at least seven other proteins called gemins 2 through 8. This structure plays a key role in the assembly of small ribonucleic proteins (snRNPs) which function as spliceosomes. The SMN complex in the nucleus co-localizes with Cajal bodies involved in transcription and processing of nuclear RNAs. Cytosolic SMN is found in axons and growth cones, as well as the neuromuscular junction. The cytosolic and peripheral actions of the SMN protein have not been fully elucidated. Researchers debate whether the deficiency of SMN produces a primary "central" or peripheral dysfunction. Several excellent reviews of this complex subject are available.

**CLINICAL FEATURES**

Classic infantile Type 1 SMA is characterized by early onset of disease symptoms. The disease clearly begins prenatally, but the first two trimesters of pregnancy are usually uneventful. Approximately one-third of mothers report a decrease in fetal movements in the third trimester of pregnancy. Neonates may be totally asymptomatic or may demonstrate obvious symptoms at birth. Early symptoms include hypotonia, muscle atrophy, generalized weakness, respiratory insufficiency, and bulbar dysfunction interfering with oral feedings.

The major manifestations of SMA relate to death or dysfunction of MNs in the anterior horn of the spinal cord and lower brainstem. There is no obvious involvement of facial musculature, nor is there ever involvement of extraocular muscles. This results in a bright, responsive facial expression and "precocious" social interaction. The evolution of bulbar weakness may make feeding precarious with risks of aspiration pneumonia. Quivering tongue movements (tongue fasciculations) are a critical diagnostic feature of Type 1 SMA. However, as a caveat to the pediatric neophyte, quivering tongue movements in a crying baby are notoriously difficult to interpret. Visible and tactile fasciculations of limb muscles are virtually never identified, due in part to overlying adipose tissue present in all but the most emaciated infants. However, quivering movements of outstretched fingers (polymini-myoclonus) is frequently seen in Type 1 and Type 2 SMA children. Profound impairment of head control in both prone and supine positions is universally encountered and is a very early manifestation of motor compromise. Type 1 SMA infants tend to assume a characteristic posture cruelly termed the "pithed frog leg position." The infant's thighs are flexed at the hip and markedly externally rotated; the knees and ankles are flexed. Upper extremity posture is characterized by arm abduction, internal rotation of the shoulders, and flexion of the elbows. Although limb weakness is generalized, it is nearly always more obvious in proximal muscle groups, and leg involvement is more severe than arms. Unlike children with central hypotonia, noxious stimulation does not result in an augmentation of spontaneous or withdrawal movement.
The respiratory pattern of children with type 1 SMA is characteristic and nearly pathognomonic. Due to severe weakness of intercostal muscles, the chest wall assumes a flattened and “bell shaped” configuration. This is accentuated by relative preservation of diaphragm function. With each inspiration, the anterior thorax retracts and the abdomen rises, reflecting diaphragmatic descent.

Therapeutic interventions in SMA are addressed below. The various aspects of supportive care directly mirror motor deficits as described. The single greatest threat to Type 1 SMA children is respiratory insufficiency complicated by atelectasis and aspiration pneumonia. Bulbar dysfunction oftentimes compromises oral intake, culminating in malnutrition. Long-term Type 1 SMA survivors almost invariably develop orthopedic deformities that include heel cord contractures and scoliosis. A comprehensive consensus statement regarding the standard of care for SMA patients was recently published and provides important guidelines for health care providers and caregivers of children with SMA.

**Laboratory Diagnosis**

Prior to the development of sensitive molecular DNA testing, the diagnosis of all types of SMA was based on clinical suspicion substantiated by EDX and muscle biopsy findings. In the majority of cases, DNA testing has replaced electromyography (EMG) and muscle biopsy as the definitive diagnostic procedure. Screening tests with CK are normal or are only slightly elevated (<3 times the upper limits of normal). EDX studies are rarely performed as the initial diagnostic investigation in infants manifesting the classic clinical Type 1 phenotype, but are very helpful when the clinical diagnosis is less certain. Sensory nerve conduction studies (NCSs) are stated in most text books to be “uniformly normal” and is true in most cases of Type 1 SMA. However, very severe cases of Type 1 SMA, usually associated with the molecular genetic correlate of a single SMN2 gene, may demonstrates the EDX phenotype of a profound sensory and motor axonal neuropathy. Motor NCSs usually reveal decreased compound muscle action potential amplitudes, reflecting decreased MU numbers. Motor nerve conduction velocities are either normal or slightly reduced, reflecting a loss of the fastest conducting motor axons. Needle EMG demonstrates abnormal insertional activity with fibrillations and positive waves. There is decreased MU recruitment of rapidly firing MUs (many of which are temporally unstable to delay line analysis). In cases characterized by profound motor deficits and compromised reinnervation, MU amplitude and duration are quite variable. True fasciculations are rarely seen in type 1 SMA.

Muscle biopsy reveals large group atrophy with whole fascicles of tiny muscle fibers. These alternate with hypertrophic mini-fascicles usually comprised entirely of type 1 muscle fibers.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of SMA includes other autosomal recessive SMA syndromes such as SMARD, due to mutations of the µ-immunoglobulin binding gene. SMARD differs from the classic SMA1 due to early involvement of the diaphragm and a gradient of distal as opposed to proximal muscle weakness. An X-linked form of SMA has been documented in several, nonrelated families. Recently, mitochondrial diseases producing an SMA picture have been reported. Two distinct syndromes including defects of the synthesis of cytochrome oxidase 2 (SCO2) gene has been delineated. These present as atypical SMA1; the findings of lactic acidosis and hypertrophic cardiomyopathy are the clues that separate this disorder from classic SMA. A mitochondrial depletive syndrome due to thymidine kinase 2 (TK2) may also produce a Type 1 SMA phenotype.

**Clinical Trials**

The molecular understanding of the pathophysiology of SMA is incomplete. The hope is that populations of impaired, but potentially viable MNs will respond to appropriate therapeutic intervention. Empiric strategies utilizing neuroprotective drugs to facilitate anterior horn cell rescue have included trials of riluzole and gabapentin, but the results have been disappointing. Current therapeutic efforts have focused upon increasing SMN2 function. A murine model has been developed with knock out of the SMN1 gene and introduction of variable copy numbers of the human SMN2 gene. Transgenic mice who harbor multiple copies of the human SMN2 gene are clinically “nearly normal.” Drugs that increase SMN2 function by upregulation of the gene include histone deacetylase (HDAC) inhibitors. Trials of HDAC inhibitors such as valproic acid, hydroxyurea, and phenylbuterate are currently underway. The use of antisense oligonucleotides to force inclusion of exon 7 in the SMN2 mRNA is under investigation. The development of high throughput screening techniques facilitates preclinical screening of hundreds of thousands of small molecules which may have a salutary effect on either SMN2 upregulation or splicing modulation to promote the translation of full length SMN protein.

**REHABILITATION AND MANAGEMENT ISSUES IN SMA**

The care of patients with SMA is often complex with many medical issues to consider. When possible, a multidisciplinary team approach is an effective way to care for SMA patients. A current understanding of the clinical management and rehabilitative care of patients with SMA will be reviewed.

**Bulbar Dysfunction and Swallowing Problems**

Bulbar dysfunction is more commonly observed in Type 1 SMA, but can also occur in Type 2 SMA and Type 3 patients especially during the later stages of the disease. Such bulbar involvement leads to problems in buccal and pharyngeal propulsion activities during eating, and it can also contribute to impaired airway protection. The prevalence of self-reported symptoms of swallowing difficulty in 85 Type 2 SMA and III patients was 36.5% in one study. Fluoroscopic swallowing evaluations in four Type 1 SMA patients revealed involvement of both the anterior and posterior phases. Impairment of facial musculature in SMA results
in weakened mastication. In addition, SMA patients have been found to have abnormal craniofacial growth patterns. The malocclusion of teeth has been attributed to various factors including weakness of masticatory muscles, tendency for mouth breathing, and poor head positioning. Management of malocclusion in SMA patients may be important for optimal nutrition and respiratory function.

**Body Composition and Nutrition**

Patients with Type 1 and Type 2 SMA are often of small stature and have greatly diminished muscle bulk. Magnetic resonance imaging of limbs has demonstrated severe muscular atrophy in Type 1 SMA and Type 2. In addition, increased subcutaneous fat is observed in these patients. In comparison, muscles of Type 3 SMA patients showed less atrophy but significant fatty infiltration. In these more chronic cases, the use of skin fold measurements may not accurately reflect the percentages of lean and fat mass.

Diffuse weakness, bulbar dysfunction, and/or respiratory distress may affect feeding in SMA patients. Therapeutic modifications may include use of a premature baby nipple with a large opening, use of proper head and jaw position along with a semi-reclined trunk position, and use of frequent small feedings to minimize fatigue. The use of larger bolus feeds may distend the stomach and encroach upon the diaphragm. Improved nourishment and nutritional status in individuals with SMA has shown to lead to a feeling of well being and a better quality of life. Poor nutritional status, labored feeding, and/or symptoms of dysphagia are indications for initiation of supplemental enteral feedings via nasogastric tube or gastrostomy. Suplemental enteral feedings may be performed by bolus, gravity drip, or continuously during the night via a pump. Another common issue facing SMA patients is constipation. This is especially problematic for infants. Constipation is thought to be caused by combination of weak abdominal muscles and immobility. Chronic constipation and impaction can further decrease the already impaired lung function, as well as decrease oral intake in these patients. Appropriate dietary management and hydration that is supplemented with laxatives, are effective in the maintenance of optimal bowel care for affected patients.

**Pulmonary Function Testing and Respiratory Management**

Restrictive lung disease is the most common and serious complication facing patients with SMA. In general, the severity of restrictive lung disease is proportional to weakness and functional class of SMA. It is most severe in infants with Type 1 SMA, while it may not affect patients with Type 3 SMA. Samah and colleagues showed that absolute forced vital capacity (FVC) was significantly related to height index and functional level in 5 to 18 year olds with SMA. Ambulatory patients showed normal or near normal values, while nonsitters showed the lowest values, with absolute FVC less than 1 to 1.56 liters. A need for ventilatory support through intermittent positive pressure breathing (IPPB) was directly related to FVC and functional status. Two thirds of those who could only sit supported used IPPB compared to only 5% of those who walked independently. Carter and colleagues showed significant reductions in FVC over time with increasing disease durations in Type 2 SMA, but not in Type 3 SMA subjects. In addition, Type 2 SMA patients showed relatively more severe declines in maximal expiratory pressure (MEP) versus maximal inspiratory pressure (MIP), suggesting relative diaphragmatic sparing.

Progressive restrictive lung disease in Type 3 SMA was shown to be relatively mild and rarely necessitated the institution of ventilatory support.

Although no specific spirometry parameters for beginning ventilatory support have been established, it has been found that the institution of mechanical ventilation in Type 2 SMA was generally not required until FVC was about 20% of the predicted value. This parameter is not absolute and ventilatory support has been initiated at FVC values in the mid-30% range. Other useful pulmonary function measurements include MIP, MEP, and peak cough flow. When these values decline, it can be indicative of poor airway clearance function, increased risk for infection, and hastened respiratory failure. In most specialty NM disease clinics, spirometry evaluation is typically performed at least annually for those SMA patients with impaired lung function (and 6 months or more frequent for those at higher risk). Children older than 5 years can usually cooperate and follow directions reliably enough to perform spirometry.

Over the last decade, advances in noninvasive ventilation technology, increased variety of ventilation interface devices, and miniaturization of ventilators leading to better portability have all contributed to improved pulmonary management of patients with SMA. Treatment of severe respiratory insufficiency in SMA may utilize noninvasive intermittent positive pressure ventilation (NIPPV) via oral and/or nasal interfaces, nasally applied bi-level positive airway pressure (BiPAP), or positive pressure mechanical ventilation via a tracheostomy. In any method, the most important factor is to obtain a good seal around the interface. The noninvasive ventilation method is particularly convenient for nighttime use. In general, nocturnal NIPPV appears to be effective for sleep-disordered breathing and nighttime hyperventilation encountered in patients with various NM diseases. In most cases, BiPAP mode of ventilation rather than continuous positive airway pressure (CPAP) is appropriate for restrictive lung volume processes secondary to progressive NM diseases. However, CPAP may have a role, particularly in young infants with Type 1 SMA who are unable to effectively synchronize with BiPAP. In all cases, frequent monitoring for adequate mask fit and appropriate ventilator pressure level settings is necessary.

Continuous invasive ventilatory support via tracheostomy should be considered when contraindications or patient aversion to noninvasive ventilation are present, or when noninvasive ventilation is not feasible due to severe bulbar weakness or dysfunction. In these cases, discussions following careful consideration of the patient/family’s desires, child’s prognosis, and child’s quality of life can often lead to a satisfactory resolution. For those SMA patients requiring full-time ventilatory support, portable ventilators can
now be easily attached to power wheelchairs, markedly improving quality of life for these patients in the community.

Secretion management and airway clearance are also very important aspects of respiratory care in SMA patients. Manual cough assist techniques performed by a caregiver, family member, or mechanical insufflator-exsufflators (cough-assist machines) can help improve airway clearance and secretion management. In addition, use of these methods in conjunction with noninvasive ventilation pre- and postoperatively have helped significantly to improve the pulmonary care of patients with SMA that are undergoing surgery. Intrapulmonary percussive devices and ventilators are available to help mobilize secretions and improve pulmonary hygiene.

Sleep disordered breathing and nocturnal alveolar hypoventilation are manifestations of worsening restrictive lung disease and respiratory failure in SMA. Sleep disordered breathing is now recognized as a significant cause of morbidity in SMA. Common signs and symptoms that suggest sleep-disordered breathing include nightmares, morning headaches, and daytime drowsiness. A polysomnography with continuous CO₂ monitoring is helpful in determining sleep-related hypoventilation. However, a nocturnal pulse oximetry in the home environment can serve as an acceptable screening tool for sleep-related oxyhemoglobin desaturation and alveolar hypoventilation when polysomnography is unavailable. Other general measures for patients with restrictive lung disease include yearly influenza and pneumococcal vaccination. A recent update regarding respiratory care of patients, as well as a consensus statement for standard of care in SMA, are available for more information and detail.

Spine Deformity

Scoliosis has been estimated to occur in 78% to nearly 100% of Type 2 SMA patients. Scoliosis almost always begins in the first decade of life as a result of severe truncal weakness. The curves are collapsing in nature and are either thoracolumbar (62%), thoracic (12%), lumbar (10%), or double curves involving thoracic with lumbar or thoracic with thoracolumbar (16%). The average deformity observed over 10 studies was 90 degrees with a reported range from 20 degrees to 164 degrees. Severe kyphosis may be a common associated deformity and virtually all patients with severe scoliosis have significant pelvic obliquity. In contrast, Type 3 SMA patients who are ambulatory have less scoliosis with reported prevalence of 8% to 63%. Spinal bracing is generally used in SMA patients who are unable to walk or to improve sitting balance. However, bracing has been repeatedly shown to be ineffective in preventing eventual progression of the scoliosis. In addition, there is concern with bracing that it may compress the rib cage and further impair the pulmonary function by lowering the vital capacity.

Spinal fusion surgery is the only effective treatment for scoliosis in SMA. For children over the age of 10 years with curves exceeding 60 degrees, instrumentation with posterior fusion is the definitive choice. Most consider improved cosmesis, balance, and comfort in the sitting position to be the primary goals of surgery. Segmental sublaminar wiring with Harrington rods, or more recently Luque instrumentation, has resulted in an average correction of approximately 50%, with maintenance of the correction continuing for years after surgery. Anterior surgical approaches in SMA patients can result in significant respiratory difficulty postoperatively and diminished pulmonary function over the long-term. Nocturnal pulse oximetry can provide valuable information about potential post-operative ventilation needs. In those patients at risk, pre-operative mask-fitting and initiation of NIPPV can improve post-operative respiratory recovery. Postoperative management after scoliosis surgery includes early involvement of physical and occupational therapies, mobilization out of bed when clinically stable, pain control, ventilatory support as needed, and appropriate pulmonary toilet. As in other NM diseases, spinal arthrodesis does not significantly improve the restrictive lung disease component of SMA by increasing the FVC.

Decline in some functional activities can occur after spinal arthrodesis. The most common includes decreased gross motor skills, transfer ability, self-feeding, hygiene, dressing, independent toileting, and ambulation. Spinal fixation may impair both compensatory lumbar lordosis and lateral trunk sway which are used by ambulatory patients to compensate for proximal weakness. Therefore, surgery is best deferred until ambulatory function loss is imminent or already lost. Patients and care providers should be adequately informed about possible short-term and long-term functional consequence of spinal arthrodesis.

Hip Dislocations and Contractures

Nonambulatory SMA patients have a high incidence of coxa valga of the proximal femur and hip subluxation. Frank hip dislocation associated with pelvic obliquity is commonly noted. Significant pain associated with hip subluxation or dislocation is rare. Operative treatment of hip subluxation or dislocation in SMA appears to be poor with a high recurrence rate. Current consensus is nonoperative conservative management. Contractures are problematic in Type 2 and Type 3 SMA patients who have lost ambulatory function. Reductions in range of motion (ROM) by greater than 20° were found among 22% to 50% of Type 2 SMA subjects. Hip, knee, and wrist contractures are the most common. Patients with SMA perceive their elbow flexion contractures to hinder one or more daily functions and the contractures were reported to be associated with greater discomfort. Occupational and physical therapy referral, as well as daily home stretching program with caregivers, should continue to prevent formation of significant joint contractures. Serial casting for contractures can be used, but a clear and practical goal for improved ROM should be kept in mind.

Osteopenia and Fractures

Osteopenia is a common finding among SMA patients. Fractures at birth may occur in SMA. Falls may also lead to fractures in SMA after seemingly trivial trauma. In one series, fractures occurred in 15% of Type 2 SMA cases and 12% of Type 3 SMA subjects. Bone mineral density is significantly reduced in SMA, and the nature of bone mineralization at the epiphysis as compared
to the diaphysis may be different. A recent study of bone density in SMA patients by dual energy x-ray absorptiometry (DEXA) scan suggests that osteopenia may be secondary to factors other than immobility.28 Currently, there are studies that suggest SMN protein’s possible role in bone remodeling.29,43 Rigid cast immobilization of fractures should be avoided to prevent a cycle of worsening osteopenia and further fractures. Calcium and vitamin D supplementation is reasonable based on DEXA results.

**Interventions to Improve Function**

Interventions designed to improve functioning of SMA patients depends on each patient’s disease severity, level of weakness, comorbidity, and patient/family goal. For nonambulatory children with SMA, early referral to a pediatric occupational and physical therapist for evaluation of appropriate adaptive equipment for self-care, seating systems, and mobility devices is important. In general, the evaluation for power wheelchair mobility can be explored as early as 18 to 20 months of age. Evaluations for adaptive equipment used for dressing, feeding, and self-care should take place when appropriate, yet frequently enough to challenge the patient’s functional skills and improve independence. For patients with adequate truncal control, but without enough strength for functional ambulation, reciprocal gait orthoses or a light-weight knee ankle foot orthosis can be considered for standing and therapeutic exercises. Standing frame and mobile stander with ankle foot orthosis may also be options for children who do not have sufficient strength to participate in standing activities. For ambulatory SMA patients, based on an individual’s functional level, judicious use of an ankle foot orthosis, a walker, a scooter, and a power wheelchair can improve community mobility function and independence.

**CONCLUSION**

Human SMA presents a unique clinical challenge. Following a period of initial decline, patients may remain clinically stable for protracted periods of time. Therefore, therapeutic endpoints and outcome measures are difficult to define.27 For a child with SMA1, the obvious target endpoints would include duration of survival and freedom from continuous mechanical ventilator support. For children with a less severe Type 2 and Type 3 SMA phenotypes, entirely different sets of outcome measures will be needed.18 The National Institute of Health has recognized that the understanding of the basic cellular pathology of SMA has reached the brink of promising clinical translation and has designated SMA as a paradigm disorder for the development of small molecule therapies. Hopefully, more effective therapies will soon be available to SMA patients that target the basic cellular mechanisms of their disease with the care of patients with SMA requires a coordinated multidisciplinary approach.

**CASE STUDY, DISCUSSION, DIAGNOSIS REFERENCES**


REHABILITATION AND MANAGEMENT REFERENCES


Myeloneuropathy

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CASE DESCRIPTION

History

A 63-year-old woman was evaluated in the multiple sclerosis clinic for a 3-month history of intermittent hand numbness and tingling. The initial clinical impression of a carpal tunnel syndrome was not substantiated on nerve conduction studies (NCSs). One month following the hand paresthesias, she noted that neck flexion would trigger an electric tingling sensation from her neck down the spine and into both upper and lower extremities. For the same duration, she had noted distal lower limb tingling and imbalance that worsened in the dark.

Examination

Mental status and cranial nerves were normal. Strength was normal except for mild weakness of intrinsic hand muscles. Sensory testing revealed mild glove-and-stocking distribution loss of light touch and pain sensation with moderate reduction of proprioception, and vibration in the toes and fingers. Upper limb coordination, as assessed by the finger-nose test, showed worsening with eyes closed (more so on the right side). Deep tendon reflexes were brisk except the ankle jerks which were depressed on the left and absent on the right. The plantar response was flexor. Romberg test was positive. Her gait was cautious and worsened significantly when walking tandem. Her only medication was gabapentin, 900 mg a day, in three divided doses.

Prior Studies

Brain magnetic resonance imaging (MRI), including gadolinium-enhanced T1 weighted images, was normal. MRI of the cervical spine revealed an increased signal on the T2-weighted sequence that involved the posterior paravertebral cervical cord and extended from C2 to C6. Also present were moderate spondylotic changes from C3 to C6. MRI of the thoracic spine was normal. The initial clinical consideration of multiple sclerosis led to a cerebrospinal fluid examination and visual evoked potential studies, both of which were unremarkable. Somatosensory evoked potential (SEP) studies showed a central conduction delay that localized to the cervical segments.

Current Studies

Routine biochemical studies were unremarkable. Her hematologic group was normal except for a slight macrocytosis (mean corpuscular volume 101.2 fl, normal: 81.6-98.3 fl). Serum vitamin B₁₂ was on the lower side of the normal range at 211 ng/L (normal: 180-914 ng/L). Serum methylmalonic acid was elevated at 0.51 µmol/L (normal: 0.08-0.46 µmol/L) and plasma homocysteine was within normal limits. Further investigations done to identify the cause of the low-normal vitamin B₁₂ included intrinsic factor antibodies which were positive.
DIFFERENTIAL DIAGNOSIS

The distal paresthesias in the case presented could have been explained by peripheral nerve dysfunction alone. Impaired distal proprioception/vibration and brisk reflexes suggest localization to the spinal cord with dorsal column and corticospinal tract involvement, respectively. Worsening of gait in the dark, a positive Romberg, and the presence of Lhermitte phenomenon, are all manifestations of dorsal column involvement. The absence of significant lower limb weakness indicates that her walking difficulty is primarily due to dorsal column involvement. MRI shows increased signal involving the dorsal column in the cervical cord. SEP studies show central conduction delay that localizes to the cervical segment. The glove and stocking distribution of symptoms and the reduced ankle jerks suggests some peripheral nerve involvement. The patient most likely has a myeloneuropathy and a related differential diagnosis.

The differential diagnosis discussed here excludes causes of myelopathy in which peripheral nerve involvement is not seen. Compressive, inflammatory-infectious, vascular, and traumatic causes of a myelopathy are, therefore, not included. Conditions such as sarcoidosis, connective tissue disorders, and paraneoplastic disease can have variable cord and peripheral nerve involvement. These conditions may merit consideration in some situations. The focus of the differential diagnosis in this case is on metabolic-toxic and hereditary disorders. Many of these conditions have clinical, electrophysiological, and neuropathological similarities. Dorsal column involvement results in impaired position and/or vibration perception and sensory ataxia. Corticospinal tract involvement may lead to weakness, spasticity, hyperreflexia, extensor plantar responses, or sphincteric dysfunction. Variable degrees of peripheral nerve and/or optic nerve involvement may be present. While therapy-related improvement may occur in metabolic myelopathies, a common outcome of therapeutic intervention is cessation of progression. Electrophysiological studies may show evidence of central conduction delay, at times with variable peripheral nerve involvement. A term that has been used to describe some of these myelopathies is central-peripheral distal axonopathy. Use of this term emphasizes the fact that in “dying back disorders” both the central nervous system (CNS) and peripheral nervous system (PNS) display a distal axonal degeneration. Loss of dorsal root ganglion cells results in axon loss in the peripheral nerves and spinal cord. The distal part of the dorsal column in the cervical cord, distal part of the corticospinal tract in the lumbar cord, and distal peripheral nerves are preferentially involved.

Myelopathies that have a metabolic basis are commonly due to specific nutrient deficiencies (e.g., subacute combined degeneration of the cord due to vitamin B12 deficiency). Some metabolic myelopathies have a hereditary basis (e.g., spinal xanthomatosis). Three forms of hereditary myelopathies are recognized: those that have a pure or predominantly motor phenotype (e.g., hereditary spastic paraplegia [HSP]), those with a predominantly ataxic phenotype (e.g., Friedreich ataxia [FA]), and those with a white matter or leukodystrophy phenotype (e.g., adrenomyeloneuropathy [AMN]). The identification of new genes and loci has blurred the distinction between these three categories. With the exception of some forms of hereditary spastic paraparesis, myelopathy or myeloneuropathy is rarely the only manifestation in hereditary disorders. It can be the presenting manifestation or predominant manifestation during a stage of the disease process. Not infrequently, the MRI in these conditions can be normal or show nonspecific findings such as cord atrophy. The presence of a signal change involving the dorsal column or corticospinal tract can help limit the associated differential diagnosis.

The references provided are restricted to those from the past 5 years. Included in the references are review articles and book chapters that can direct the interested reader to more detailed bibliographies.

MYELONEUROPATHIES DUE TO SPECIFIC NUTRIENT DEFICIENCY

Vitamin B12 Deficiency and Related Conditions

Neurological signs and symptoms may be the earliest manifestation of vitamin B12 deficiency and not infrequently have a subacute onset. They may be unaccompanied by hematological manifestations such as anemia, macrocytosis, neutrophil hypersegmentation, or megaloblastic marrow changes. Neurological manifestations may include a myelopathy with or without an associated peripheral neuropathy, cognitive impairment, optic neuropathy, autonomic dysfunction, paresthesias without abnormal signs, and rarely leukoencephalopathy. Symptom onset may be in the hands; concomitant involvement of the upper and lower limbs may be seen. Less common neuroimaging findings include contrast enhancement involving the dorsal and lateral columns, decreased dorsal column signal on T1-weighted images, and cord swelling.

Though a widely used screening test, serum vitamin B12 measurement has technical and interpretive problems and lacks sensitivity and specificity for the diagnosis of vitamin B12 deficiency. Serum vitamin B12 can be normal in some patients with vitamin B12 deficiency, and serum methylmalonic acid and total homocysteine levels are useful diagnostic studies. One third of individuals with low-normal vitamin B12 levels may have elevated methylmalonic acid and/or homocysteine levels. Methylmalonic acid is at least as sensitive as homocysteine for the diagnosis of vitamin B12 deficiency but has superior specificity. Folate deficiency can cause an elevation in homocysteine levels. Elevated methylmalonic acid and homocysteine levels may also be seen in renal insufficiency and rare genetic disorders.

Despite extensive investigations, the cause of vitamin B12 deficiency often remains unknown. Vitamin B12 deficiency commonly results from reduced gastrointestinal absorption. The incidence of vitamin B12 deficiency increases with age and is due to accompanying hypochlorhydria. This is because an acidic environment in the stomach is needed for vitamin B12 to be released from food. Pernicious anemia, a prior history of gastric surgery
(bariatric surgery, surgery for peptic ulcer disease), and other causes of malabsorption (ileal disease, pancreatic insufficiency, bacterial overgrowth) are additional etiologies of vitamin B₁₂ deficiency. Pernicious anemia is associated with positive intrinsic factor antibodies. Other laboratory findings of limited specificity in pernicious anemia include an elevated serum gastrin, decreased pepsinogen I, and gastric parietal cell antibodies. Despite the fact that methionine synthase requires folate as a cosubstrate, for reasons that are not understood, neurological complications due to folate deficiency are rare and controversial. Folate deficiency often coexists with other nutrient deficiencies. The megaloblastic anemia due to folate deficiency is indistinguishable from that seen in vitamin B₁₂ deficiency. Nitrous oxide (“laughing gas”) is a commonly used inhalational anesthetic agent that has been abused due to its euphoriant properties. It is a potent oxidizing agent that produces irreversible oxidation of the cobalt core of cobalamin and renders methylcobalamin inactive. Earlier reports of nitrous oxide toxicity were among dentists, medical or nursing staff working in poorly ventilated surgeries, and in patients with a borderline vitamin B₁₂ status after prolonged nitrous oxide anesthesia. More recently, the practice has been seen among university students. Neurological manifestations may be seen despite a normal vitamin B₁₂ level. Signs and symptoms appear relatively rapidly with nitrous oxide toxicity but may be delayed by a few weeks after acute exposure. Increased prevalence of vitamin B₁₂ deficiency has been recognized in human immunodeficiency virus (HIV) infected patients with neurological symptoms. The histopathology of acquired immune deficiency syndrome (AIDS) associated myelopathy resembles that of subacute combined degeneration seen in vitamin B₁₂ deficiency. The pathogenesis in many cases of AIDS-associated myelopathy may not be related to direct HIV infection of the spinal cord.⁴

In the case presented, the clinical presentation and neuroimaging are consistent with the subacute combined degeneration that is seen with vitamin B₁₂ deficiency. Her low-normal vitamin B₁₂ levels suggest that the neurologic manifestations could be due to vitamin B₁₂ deficiency. The elevated methylmalonic acid levels confirmed metabolically significant vitamin B₁₂ deficiency. The underlying cause of vitamin B₁₂ deficiency in her case is pernicious anemia.

**Copper Deficiency**

The most common manifestation of acquired copper deficiency is a myelopathy or myeloneuropathy that resembles the subacute combined degeneration seen with vitamin B₁₂ deficiency.⁴ Also described is asymmetric motor weakness and atrophy with sensory signs or symptoms and electrodiagnostic (EDX) evidence of diffuse denervation.⁵ Hematological manifestations of acquired copper deficiency (anemia, neutropenia, and a left shift in granulocytic and erythroid maturation) are not always present. Spinal cord MRI in patients with copper deficiency myelopathy may show increased signal on T₂-weighted images in the paramedian cord, most commonly cervical. Copper deficiency-associated myelopathy has been described in various animal species. Often seen in ruminants, it has been referred to as “swayback” or enzootic ataxia.

Because of copper’s ubiquitous distribution and low daily requirement, acquired dietary copper deficiency is rare. Copper deficiency may result from malabsorption, excess zinc ingestion, and inadequate supplementation during enteral or total parenteral nutrition. Not infrequently, the cause for copper deficiency is not known. Of the known causes of acquired copper deficiency, the most common is a prior history of gastric surgery. As stated earlier, a prior history of gastric surgery is also a risk factor for B₁₂ deficiency. In a recent series of post-bariatric surgery related neurological complications, myelopathy due to copper and/or vitamin B₁₂ deficiency was noted as the most commonly seen neurological complication.¹⁰ A low serum copper does not imply copper deficiency. Wilson disease, a disease of copper toxicity, is also associated with a low serum copper. In Wilson disease, urinary copper excretion, free serum copper, and copper content in the liver and brain is elevated. A low serum copper can also be seen in some carriers of the Wilson disease gene. Aceruloplasminemia, a disorder of iron metabolism, is also associated with a low serum copper despite there being no disturbance in copper metabolism.

Copper and vitamin B₁₂ deficiency can coexist. Both may be associated with hematologic manifestations with or without neurologic derangement. Continued progression of symptoms in patients with a subacute combined degeneration due to vitamin B₁₂ deficiency despite adequate vitamin B₁₂ replacement should prompt a search for underlying copper deficiency.

**Vitamin E Deficiency**

Neurologic manifestations of vitamin E deficiency include a progressive spinocerebellar syndrome with peripheral neuropathy and dorsal column dysfunction. Clinical features include gait difficulty, hypo- or areflexia, pyramidal signs, impaired position and vibration perception, dysarthria, ophthalmoplegia, and pigmentary retinopathy.¹⁴,¹⁵,²⁴ The clinical presentation may be similar to that of subacute combined degeneration or Friedreich ataxia. MRI may show high-signal lesions on T₂-weighted images in the posterior columns.

In patients with neurological manifestations due to vitamin E deficiency, the serum vitamin E levels are frequently undetectable. Serum vitamin E levels are dependent on the concentrations of serum lipids. Hyperlipidemia or hypolipidemia can independently increase or decrease serum vitamin E, respectively, without reflecting similar alterations in tissue levels of the vitamin. Serum vitamin E concentrations may be artificially decreased in the normal range in patients with vitamin E deficiency due to cholestatic liver disease, a condition in which lipid levels are often elevated.

Vitamin E deficiency in adults may be due to gastrointestinal, pancreatic, or hepatic disease. In addition to these causes, particularly in children, vitamin E deficiency may be seen due to genetic defects in α-tocopherol transfer protein (ataxia with vitamin E deficiency), apolipoprotein B (homozygous hyperbetalipoproteinemia), microsomal triglyceride transfer protein (abetalipoproteinemia or Bassen-Kornzweig disease), or due...
TROPICAL MYELONEUROPATHIES

The term tropical myeloneuropathies has been used to describe a number of conditions seen in several developing countries. Often the precise cause is unknown but has been considered to be nutritional or toxic. Two major categories recognized in the past were patients with prominent sensory ataxia (tropical ataxic neuropathy [TAN]), and those with prominent spastic paraparesis (tropical spastic paraparesis [TSP]). The term TAN was originally used to describe an ataxic neuropathy with optic atrophy seen in Nigeria which was related to chronic cassava consumption and related cyanide exposure. Human T-cell lymphotropic virus, type I (HTLV-I) myelitis had been called TSP in many equatorial regions and HTLV-I-associated myelopathy in Japan. HTLV-II is also recognized to cause a chronic myelopathy that resembles TSP. In addition to TSP, other neurologic manifestations of HTLV-1 infection include a myopathy, peripheral neuropathy, cognitive impairment, and an amyotrophic lateral sclerosis-like (ALS) syndrome. Subacute-myelo-optico-neuropathy (SMON) is a myeloneuropathy with optic nerve involvement that affected individuals in Japan, and elsewhere, to a lesser degree between 1955 and 1970. Epidemiological studies have suggested that SMON was the result of toxicity from the antiparasitic drug clioquinol. SMON was characterized by subacute onset of lower limb paresthesias and spastic paraparesis with optic atrophy. Tendon hyperreflexia and extensor plantar responses were seen though at times the ankle jerk was absent. The precise mechanism of action of clioquinol has been unclear. Clioquinol is a copper chelator. Identification of a myelopathy resulting from acquired copper deficiency has led to speculation that clioquinol-induced neurotoxicity could have been a consequence of copper deficiency. From 1991 to 1994, an epidemic in Cuba affected more than 50,000 people and caused optic neuropathy, sensorineural deafness, dorsolateral myelopathy, dysautonomia, bulbar dysfunction, and axonal sensory neuropathy. Identified risk factors included irregular diet, weight loss, smoking, use of alcohol, and excessive sugar consumption.

TOXIC MYELONEUROPATHIES

The signs and symptoms of acute organophosphate toxicity are due to acetylcholinesterase inhibition and resulting muscarinic and nicotinic dysfunction. In some patients, after resolution of the cholinergic crisis, an intermediate syndrome develops. This is likely a neuromuscular junction defect characterized by weakness of neck flexors, proximal limb, and respiratory muscles. Organophosphate induced delayed neurotoxicity occurs 1 to 3 weeks after acute exposure and after a more uncertain duration of chronic exposure to certain organophosphate compounds. It may occur in the absence of the cholinergic or intermediate phase. The symptoms include distal paresthesias, progressive leg weakness and wasting, and cramping muscle pain. There may be evidence of upper limb involvement and pyramidal tract dysfunction. Sensory loss is mild when present. N-hexane and methyl-n-butyl ketone are hexacarbons that were commonly used in industrial solvents and household glues. More recently, the most common source of n-hexane exposure has been intentional inhalation of household glues for intoxication (“glue-sniffer’s neuropathy”). These hexacarbon solvents are metabolized to 2,5-hexanedione which is largely responsible for their neurotoxicity. Methyl ethyl ketone may be present in solvent mixtures containing n-hexane or methyl n-butyl ketone and can potentially neurotoxicity of these agents. Repeated exposures to these hexacarbons causes a progressive, symmetric, ascending, sensorimotor, distal axonopathy that may have a Guillain-Barré syndrome-like presentation. Despite cessation of exposure, continued progression may occur for weeks (“coasting”) prior to arrest and significant subsequent improvement. With improving peripheral neuropathy, evidence of central dysfunction such as spasticity may become evident. Workers exposed to monomeric acrylamide in grouting and those who handle monomeric acrylamide in the production of polyacrylamide flocculents are at risk of acrylamide neurotoxicity. Acrylamide intoxication results from dermal absorption or inhalation. Acute neurotoxicity due to acrylamide poisoning is characterized by an encephalopathy and gait ataxia that may be followed by a delayed neuropathy. A progressive, distally prominent, symmetric, dying back, large-fiber, axonal, sensorimotor neuropathy is the hallmark of chronic toxicity. The neurotoxicity is mediated by cerebellar Purkinje cell injury and by degeneration of distal axons in the PNS and CNS.

HEREDITY MYELOPATHIES OR MYELONEUROPATHIES WITH A PURE OR PREDOMINANTLY MOTOR PHENOTYPE

The HSPs are a diverse group of heterogeneous neurologic disorders in which the predominant symptom is insidiously progressive walking difficulty due to bilateral, fairly symmetric, lower limb spasticity. Additional manifestations may include urinary urgency and mild impairment of distal lower limb vibration perception. In uncomplicated or pure HSP, the spastic weakness is confined to the lower limbs. Brisk reflexes may be seen in the upper limbs, but upper limb strength and dexterity, speech, and swallowing remain unaffected. In complicated or complex HSP, additional neurologic or systemic findings may be present. These include mental retardation, dementia, ataxia, peripheral neuropathy, amyotrophy, seizures, deafness, dysarthria, ichthyosis, optic atrophy, retinitis pigmentosa, and cataracts. Symptom onset may occur at any age. Distal muscle weakness and wasting can be seen in some HSPs (e.g., SPG17 and SPG20).

The age of symptom onset, rate of progression, clinical features, and degree of disability vary between different genetic subtypes and also within the same family. This is most likely due to the existence of genetic modifiers. Autosomal dominant, autosomal recessive, and X-linked modes of inheritance are described. Autosomal dominant is the main mode of inheritance and this subgroup is predominantly associated with the pure forms. Family history may be absent due to incomplete ascertainment, de novo mutations, late symptom onset, asymptomatic carriers, and phenotypic variability with mild manifes-
tations. Almost 40 loci and 15 HSP genes have been discovered. HSP loci are designated spastic paraplegia followed by a number that indicates the order of their discovery. Genetic testing is available for some HSPs. Genetic testing typically examines coding sequences and intron-exon splice junctions. Sequence abnormalities in gene promoter and other regulatory elements are not assessed. Large deletions may not be detected by standard techniques. Additionally, the yield of identifying mutations in patients without a family history is relatively low.

While genetic confirmation is desirable, the diagnosis of HSP is often clinically made after excluding other causes. The relatively non-progressive gait pattern of some early-onset forms of HSP may resemble cerebral palsy. Extension of spasticity and incoordination to the upper limb is seen in primary lateral sclerosis and ALS, helping to distinguish these forms of motor neuron disease.

**HEREDITY MYELONEUROPATHIES WITH A CEREBELLAR PHENOTYPE**

The initial evaluation of an ataxic patient should include an assessment for acquired causes. This screening should be considered even if a hereditary cause is suspect. Most hereditary ataxias include CNS involvement beyond the cerebellum, most notably, the brainstem and spinal cord.6 The early stages are often associated with a spastic-ataxic gait. Additional features such as dementia, behavioral changes, retinopathy, pyramidal or extra pyramidal features, autonomic dysfunction, and peripheral nerve involvement may be seen as the disease progresses.

FA is the most common recessively inherited ataxia. Identification of the underlying genetic defect has revealed existence of milder forms including those with later onset (beyond 25 years). These patients lack prominent extra-CNS involvement. Reflexes may be present, and spasticity, rather than ataxia, may be the predominant manifestation. Mild cerebellar atrophy (a feature not associated with typical FA) may be seen. Hence, genetic testing for FA should be considered in adult-onset ataxias. However, the presence of prominent cerebellar atrophy in adult-onset ataxia merits consideration of the spinocerebellar ataxias (autosomal dominant), multisystem atrophy type C, or, as an exclusionary diagnosis, idiopathic late onset cerebellar ataxia. The differential diagnosis includes conditions like ataxia with vitamin E deficiency, abetalipoproteinemia, Refsum disease, cerebrotendinous xanthomatosis (including its spinal variant), mitochondrial recessive ataxia syndrome, ataxia-telangiectasia, ataxia-telangiectasia-like disorder, ataxia with oculomotor apraxia type 1 and 2, and others. Many of these disorders are rare, have a geographical predilection, and early age of onset. Later-onset presentations of ataxia-telangiectasia, and ataxia with oculomotor apraxia are being increasingly recognized. Mitochondrial disorders that are included in the differential diagnosis of ataxic syndromes include myoclonic epilepsy with ragged red fibers, mitochondrial encephalopathy with lactic acidosis and stroke, neuropathy-ataxia-retinitis pigmentosa, coenzyme Q10 deficiency ataxia, and Kearns-Sayre syndrome. Leber hereditary optic neuropathy can be associated with pyramidal-pattern lower limb weakness, dorsal column dysfunction, gaze-evoked nystagmus, visual dysfunction, and absent ankle jerks.9 MRI may show increased T2-signal involving the pontine tegmentum, inferior olives, anterior horns, and dorsal columns.

**MYELONEUROPATHIES WITH A LEUKODYSTROPHY PHENOTYPE**

The term leukodystrophies is used to describe an ever expanding group of rare neurologic disorders with defined clinical, pathological, imaging, and genetic characteristics. The dysmyelinating inherited leukodystrophies that enter in the differential diagnosis of myeloneuropathies include adrenoleukodystrophy, metachromatic leukodystrophy, globoid cell leukodystrophy, or Krabbe disease. The onset of neurologic manifestations in leukodystrophies is generally preceded by a period of normal development. The initial manifestation may be bilaterally symmetrical spasticity with weakness and ataxia. In some childhood-onset leukodystrophies, a demyelinating peripheral neuropathy may be present (e.g., metachromatic leukodystrophy, globoid cell leukodystrophy). Leukodystrophies may also be associated with cognitive and behavioral disturbances (e.g., adrenoleukodystrophy, adult-onset metachromatic and globoid cell leukodystrophy) and optic nerve involvement. Pattern recognition on MRI is a key diagnostic aid. Definitive diagnosis often requires genetic studies or pathologic confirmation. Additional testing employed in the work up of leukodystrophies include enzyme analysis on leukocytes or fibroblasts, urine for metabolic studies, skin biopsy, nerve conduction, and evoked potential studies. Despite extensive investigations, many leukodystrophies often remain undiagnosed. In context of a discussion of the differential diagnosis of myeloneuropathies, some conditions merit further explanation.

**Adrenomyeloneuropathy**

AMN is an X-linked disorder characterized by impaired oxidation of very long chain fatty acids (VLCFAs). The following phenotypes are recognized: childhood cerebral, adolescent cerebral, adult-onset cerebral, AMN, Addison only, and asymptomatic or presymptomatic.19 Over 25% of patients with adrenoleukodystrophy have the AMN form. AMN generally presents in the second to fourth decade as a slowly progressive spastic paraparesis with dorsal column and sphincteric dysfunction. Eventually, many patients with AMN may develop cerebral involvement and/or adrenal dysfunction. Fifty percent of heterozygote women develop an AMN-like syndrome and 20% of carriers have normal plasma concentration of VLCFAs. Mutation analysis may be required for diagnosis.

**Pelizaeus-Merzbacher disease.**

Pelizaeus-Merzbacher disease is an X-linked disorder caused by a defect in the proteolipid protein. The clinical spectrum includes a mild form presenting as spastic paraplegia (SPG2) with or without nystagmus and ataxia.6 Female heterozygotes may also have clinical manifestations.
Adult polyglucosan Body Disease

Adult polyglucosan body disease is a progressive neurologic disorder characterized by upper and lower motor neuron involvement. The pathological hallmark is the presence of periodic acid-Schiff positive cytoplasmic spheroids composed of branching polysaccharides (polyglucosan bodies) in the brain, spinal cord, peripheral nerves, and other organs. The clinical features include weakness, spasticity, incontinence, dementia, and peripheral neuropathy. A myelopathic presentation is recognized. MRI findings include cerebral, cerebellar, and spinal cord atrophy with extensive, confluent, nonenhancing areas of increased T2-signal involving the periventricular and subcortical white matter.

Cerebrotendinous Xanthomatosis

Cerebrotendinous xanthomatosis is an autosomal recessive lipid storage disorder characterized by impaired hepatic conversion of cholesterol to cholic and chenodeoxycholic acids due to deficiency of the hepatic mitochondrial enzyme sterol-27-hydroxylase. This leads to elevated plasma cholesterol. Cholesterol and cholestanol accumulate in affected tissues leading to cataracts, tendon xanthomas, and neurological abnormalities. Cerebrotendinous xanthomatosis presents with chronic diarrhea and cataracts in children. Neurological symptoms develop after the second decade and include pyramidal or extrapyramidal manifestations, cerebellar signs, cognitive decline, epilepsy, and neuropathy. Spinal xanthomatosis presents as a slowly progressive spinal cord syndrome without cognitive decline, cerebellar dysfunction, or tendon xanthomas. MRI may show cerebral, cerebellar, brainstem, and callosal atrophy with focal and diffuse hyperintense lesions in the cerebral and cerebellar white matter on T2-weighted images. The spinal form may also show an increased signal on T2-weighted images in the lateral and dorsal column of the spinal cord.

EVALUATION

To help the clinician sort through the diagnostic considerations outlined above, important tests such as spinal MRI, NCSs, electromyography (EMG), SEPs, and certain laboratory tests are needed.

Spinal MRI is important in excluding a structural cause for myeloneuropathy. In most cases with clinical findings of both myelopathy and polyneuropathy, the cause will be metabolic, but an MRI is important, especially in older patients, where a compressive myelopathy might coexist with a coincidental cryptogenic polyneuropathy (polyneuropathy occurs in greater than 3% of older adults). In cases of nonstructural myeloneuropathy, MRI may be entirely normal. When present, abnormalities typically consist of relatively nonspecific T2 signal changes. When spinal MRI shows white matter signal changes, brain MRI may be helpful by providing indications suggestive of a leukodystrophy.

NCSs are important for confirming the presence of neuropathy, as myelopathy alone can produce sensory impairments that mimic polyneuropathy. In addition, determining if the neuropathy is primarily axonal or demyelinating is important for guiding further workup. In most cases of myeloneuropathy, the neuropathy is axonal. Findings of demyelination would warrant evaluation for a leukodystrophy. NCS findings in adrenomyeloneuropathy are typically axonal, but demyelinating findings may be seen in other leukodystrophies such as metachromatic leukodystrophy and Krabbe disease.

Just as NCSs can help confirm the presence of neuropathy in a patient with myeloneuropathy, SEPs can be useful in confirming a spinal cord lesion in polyneuropathy patients with large fiber sensory deficits and uncertain clinical findings of myelopathy.

In patients with myeloneuropathy, laboratory evaluation for vitamin B12 deficiency is important and usually of very high yield. As previously outlined, testing for abnormalities of copper and zinc are important additions to the laboratory assessment of myeloneuropathy. Testing for these deficiencies will be described in more detail below. Vitamin E deficiency typically produces a spinocerebellar ataxia picture, but the presentation of vitamin E deficiency may resemble a myeloneuropathy. Testing serum vitamin E levels is easily done and is without pitfalls, but will be of low-yield in most cases.

Blood count findings of anemia (especially macrocytic) supports vitamin B12 deficiency. Anemia, leukopenia, or pancytopenia may be seen in copper deficiency. However, a significant number of patients with vitamin B12 or copper deficiency will have normal blood counts and indices.

Additional, potentially useful blood tests include the angiotensin converting enzyme level for sarcoid and erythrocyte sedimentation rate, antinuclear antibodies, and other serologies for collagen vascular disorders. If the clinical setting warrants, HIV serology should also be obtained. Serology for HTLV-I and HTLV-II may also be helpful in patients with a history of blood transfusion, intravenous drug use, or for those with a history of travel to the Caribbean or southeast Asia.

In young patients or those with suggestive brain MRI scans or family histories, laboratory evaluation for leukodystrophies could be undertaken. This would include assays for very long chain fatty acids and arylsulfatase.

Nerve biopsy is not routinely indicated in the evaluation of a patient with myeloneuropathy. However, it may be helpful in the diagnosis of a suspected leukodystrophy or inflammatory process. In a patient with prominent motor findings and urinary problems, biopsy may be performed to look for evidence of polyglucosan body disease.

The most likely causes for a myeloneuropathy syndrome are vitamin B12 or copper deficiency. The diagnosis of these conditions will be discussed in more detail.
**Vitamin B₁₂ Deficiency**

The standard vitamin B₁₂ assay is not always sufficiently sensitive. A significant proportion of vitamin B₁₂ deficient patients may have serum vitamin B₁₂ levels that are within the normal range.³⁰ Measurement of the serum metabolites methylmalonic acid (MMA) and homocysteine (Hcy) can significantly improve diagnosis.¹³,²⁰ Among persons with serum vitamin B₁₂ levels within the normal range, MMA and Hcy testing will reveal vitamin B₁₂ deficiency in 5% to 10% of those having a serum vitamin B₁₂ level less than 300 pg/ml, and in 0.1% to 1% of those with a serum vitamin B₁₂ level greater than 300 pg/ml.¹⁹ Among patients with polyneuropathy, serum metabolite testing will demonstrate vitamin B₁₂ deficiency in a significant number of cases in which serum vitamin B₁₂ levels are normal.²⁴,²⁹ It is unknown whether this also is the case for myeloneuropathy patients, as comparable studies have not been performed in this population.

It has been recommended that MMA and Hcy be measured in patients with serum vitamin B₁₂ levels less than 300 pg/ml.⁷ However, other authors suggest raising this cutoff to 350 pg/ml.¹⁸,²⁵ It remains uncertain whether there is a sufficiently high serum vitamin B₁₂ level above which would deem testing MMA and Hcy unnecessary. The author proposes measuring serum metabolites in all myeloneuropathy patients. If either is elevated and no alternative cause for myeloneuropathy is identified, empiric vitamin B₁₂ replacement therapy is reasonable.

Unfortunately, there are further difficulties in the laboratory diagnosis of vitamin B₁₂ deficiency. Although elevated serum levels of MMA or Hcy are rather specific for vitamin B₁₂ deficiency, there are some caveats. Hypovolemia, renal insufficiency, and certain genetic disorders can produce elevations of either MMA or Hcy.² Hypothyroidism, increased age, and deficiency of folate or pyridoxine are potential causes of elevated Hcy.² Genetic causes of MMA elevations are quite rare and vitamin B₁₂ is the only deficiency which increases MMA.

A decreased serum vitamin B₁₂ level and an elevated MMA and/or Hcy confirms the diagnosis of a vitamin B₁₂ deficiency. In the appropriate clinical setting, a normal vitamin B₁₂ level with an elevated MMA is very specific for vitamin B₁₂ deficiency. If the Hcy but not the MMA is elevated, empiric vitamin B₁₂ replacement therapy can be initiated with a repeat Hcy level obtained after several weeks. If an elevated MMA or Hcy level is secondary to vitamin B₁₂ deficiency, it will return to normal after 1 to 2 weeks of replacement therapy.³¹ Alternatively, in the case of a normal serum vitamin B₁₂ and elevated serum metabolite, confirmatory testing could be pursued. The Schilling test has traditionally been the next test used in patients who are found to have low serum vitamin B₁₂. However, most hospitals have stopped performing this test due to problems with accuracy, cost, and radiation exposure.³² Anti-intrinsic factor antibodies are extremely specific for pernicious anemia, but these antibodies are present in only about 50% of patients.³ Anti-parietal cell antibodies can be found in up to 90% of pernicious anemia patients, but have also been seen in healthy older adults.³ Elevations of fasting serum gastrin are approximately 70% sensitive and specific for pernicious anemia.²³ The combination of elevated gastrin and anti-parietal cell antibodies is highly suggestive of pernicious anemia.²²

Conditions other than pernicious anemia can produce vitamin B₁₂ deficiency. These include dietary avoidance (vegetarians), gastrectomy, gastric bypass surgery, ileal disease, pancreatic insufficiency, bacterial overgrowth and medications (such as histamine-2 blockers, proton-pump inhibitors and metformin).² No apparent cause of deficiency is identified in a significant number of patients with vitamin B₁₂ deficiency.¹⁸,²⁵ In the absence of symptomatic gastrointestinal disease, it is probably not necessary to seek a diagnosis of pernicious anemia in a patient with vitamin B₁₂ deficiency because this information will not alter management.³¹

A number of MRI findings may be seen in vitamin B₁₂ myeloneuropathy, but the MRI is often completely normal. Common MRI abnormalities include an increased T2-weighted signal in the subcortical white matter and posterior and lateral columns. Less common findings include contrast enhancement involving the dorsal and lateral columns, decreased dorsal column signal on T1-weighted images, and swelling of the cord.²⁶ NCSs play an important role in identifying myeloneuropathy. A common misperception is that the neuropathy in vitamin B₁₂ deficiency is demyelinating. This results from the fact that demyelination is seen pathologically in the spinal cord as well as from early EDX studies of vitamin B₁₂ deficiency neuropathy. In early series, only motor conduction velocities were measured.⁴,²⁰ However, in most studies employing modern NCS techniques, the neuropathy of vitamin B₁₂ deficiency has been found to be axonal.⁵,⁶,¹³,²¹,²⁹,³³ This is corroborated by findings on sural nerve biopsy.¹⁴,²¹ There are no NCS or EMG findings which, when detected in an individual patient, would suggest vitamin B₁₂ deficiency as opposed to other causes of neuropathy.²⁹

SEP's will demonstrate spinal lesions in a significant percentage of vitamin B₁₂ deficiency patients with neurologic symptoms.⁵,⁶,¹⁰,¹³,¹⁵,³³,³⁵ In some cases, SEP's may be the only test to reveal abnormalities.¹²,²⁸

**Copper Deficiency**

Copper deficiency is a much less common cause for myeloneuropathy than vitamin B₁₂. Unfortunately, the diagnostic evaluation is more straightforward: a normal serum copper level excludes deficiency. Serum zinc should also be performed as increased zinc (usually taken in the form of nutritional supplements) can cause impaired gastrointestinal absorption of copper.

Spinal MRI in patients may be normal or show increased T2 signal. In some cases, brain MRI may show white matter changes resembling demyelination.²⁷
NCSs and EMG in patients with copper deficiency myeloneuropathy typically show an axonal sensorimotor polyneuropathy, although a purely motor neuropathy has also been described.\(^8\)

**TREATMENT**

Most myeloneuropathy syndromes have no specific treatment, although vitamin B\(_{12}\) and copper deficiencies are exceptions.

**Vitamin B\(_{12}\) Deficiency**

There is no known ideal approach to vitamin B\(_{12}\) replacement. A common regimen is 100 to 1000 mcg intramuscularly (IM) for 5 to 7 days, followed by monthly 100 to 1000 mcg IM injections.\(^7\) An alternate approach is to begin with 1000 mcg IM per week for one month, followed by 1000 mcg IM per month thereafter. Some patients with vitamin B\(_{12}\) deficiency can likely be effectively treated with oral vitamin B\(_{12}\). Individuals with pernicious anemia are capable of absorbing small amounts of orally administered vitamin B\(_{12}\).\(^3\) The daily requirement for vitamin B\(_{12}\) is 1 to 2 mcg, and approximately 1% of orally administered vitamin B12 can be absorbed by patients with pernicious anemia.\(^3,17\) Therefore, an oral vitamin B\(_{12}\) dose of 1000 mcg per day should be sufficient. Several series report successful oral treatment of vitamin B\(_{12}\) deficiency.\(^3\) In a randomized trial that compared treatment with 2000 mg oral vitamin B\(_{12}\) per day to 1000 mg intramuscular vitamin B\(_{12}\) per month,\(^31\) both groups showed similar improvements in hematologic indices, serum MMA and Hcy, and neurologic symptoms. However, only 8 out of 33 subjects had neurologic symptoms and the methods used for assessing improvement are not described. Although the authors of this study could not demonstrate a superior clinical outcome in either group, the patients treated with oral vitamin B\(_{12}\) had significantly higher serum vitamin B\(_{12}\) and lower MMA levels at the study’s conclusion (4 months).\(^17\)

The author uses an oral replacement strategy in most cases, instructing patients to take 1000 mcg per day. The most common condition being treated this way is vitamin B\(_{12}\) deficiency polyneuropathy. In patients with severe neurological deficits or who are experiencing a subacute onset, a traditional parenteral replacement strategy is used. Admittedly, there are no clear data that guide this.

Approximately 1 month after beginning oral vitamin B\(_{12}\) replacement therapy, the author obtains repeat serum vitamin B\(_{12}\), MMA and Hcy levels. If these do not show normalization, patients are usually switched to parenteral therapy. Among patients initially placed on parenteral therapy, a switch to oral treatment could be tried. As long as MMA and Hcy remain normal, one can assume adequate replacement.

It is not clear whether the rate or degree of symptomatic improvement can be used as a guide to assess the adequacy of vitamin B\(_{12}\) replacement. The dogma has been that the neurological deficits of vitamin B\(_{12}\) deficiency respond rapidly to replacement therapy.\(^9\) An important consideration, however, is the duration of symptoms before treatment. Patients with longstanding symptoms are less likely to show a good therapeutic response.\(^9,11,34\) Myelopathy may respond quickly to therapy, but the response of neuropathy to treatment may be slow and incomplete.\(^29\) Even if immediate improvement is not observed, replacement therapy in vitamin B\(_{12}\) deficient patients may prevent progression.\(^20\) One other consideration regarding treatment is that in approximately 2% of patients, sensory symptoms may initially worsen during the first month of treatment before improvement is seen.\(^9\) The reason for this is not known.

**Copper Deficiency**

No specific studies have been conducted to determine the best approach to copper replacement therapy. Therefore, there is no clear consensus with respect to the ideal form, dose, route, or duration of therapy. For patients with copper deficiency induced by excess zinc intake, cessation of zinc supplementation is usually the only intervention necessary. As is also the case for vitamin B\(_{12}\) deficiency, even when copper deficiency is caused by malabsorption, oral replacement therapy is usually sufficient. As stated above, there is no clearly established regimen. The author uses the strategy employed by Kumar and colleagues at the Mayo Clinic, who have had the most experience with copper deficiency myeloneuropathy: 6 mg/d of elemental copper orally for a week, 4 mg/d for another week, and 2 mg/d thereafter.\(^16\) Repeat serum copper levels should be obtained periodically to assess the adequacy of replacement. If adequate replacement cannot be obtained with oral therapy, then cupric sulfate can be given intravenously at a dose of 2 mg per day for 5 days. Repeat courses are given as needed.

Neurological improvement following copper replacement varies. A number of myeloneuropathy patients do not show significant resolution, but further progression can be prevented.\(^26\) In contrast, hematological abnormalities typically respond quickly and fully to therapy.

**GENERAL CONSIDERATIONS FOR REHABILITATION**

Some general comments about the patient’s biomechanical status can be made based on the history and physical examination presented. A patient’s diminished ability to maintain balance in the dark is consistent with impairment in somatosensory function, with excess reliance on vision, and is the historical equivalent of the positive Romberg test on examination. An analogous historical feature with regard to the upper extremities (UE) is the inability to button effectively without view of the clothing fasteners. For example, patients with diminished UE somatosensory function often relate that they cannot fasten the top two buttons in a shirt without a mirror, this may be thought of as a UE Romberg test in that it represents a task that cannot be performed without visual input. The report of diminished proprioception at the toes makes it likely that ankle proprioceptive thresholds are increased (worse) at the ankle, if high technology quantification of these thresholds were to be obtained.\(^15\) This is of functional relevance because increased proprioceptive thresholds at the ankle are inversely related to stability in unipedal
CLINICAL MANAGEMENT OF NEUROPATHIC GAIT

Patient and Family Education

Because of its insidious onset, and the fact that patients often appear to walk reasonably well under ideal conditions, it is common for both physicians and patients to underestimate the impact of neuropathy. It is important for the physician to explain to the patient and family that the patient has lost a special sense that is likely of greater importance than vision in the maintenance of balance. They should also be informed that the rapid generation of strength in the LEs, necessary to prevent a fall is lost. They should be also be told that it takes considerable concentration for a person with neuropathy to walk and so distractions should be avoided while the patient is ambulating. If the patient is walking on a firm, flat, and familiar surface with good lighting and no distractions, then the patient is probably safe. In all other circumstances, the patient should employ UE touch of a wall, cane, other person, or use ankle orthoses that provide lateral support.

Environmental Modification

Reliable and convenient support surfaces for UE touch (which markedly increases robustness to perturbations), should be made available in the patient’s home, especially near stairs or other irregular surfaces. These need not be obvious fixtures such as grab bars, but can be pieces of furniture such as desk tops and sofa arms. Specific advice given by a visiting physical and/or occupational therapist can be of value to the patient.

Optimize Vision

With the progression of the patient’s somatosensory dysfunction, vision becomes the chief source of afferent information for maintaining postural stability. Therefore, the patient should be evaluated by an ophthalmologist to assure optimal vision. The patient should not use bifocals, even those with transitional lenses, as they have been found to be an independent predictor of falls. This effect, identified in an unselected group of older persons living in the community, is likely even more important in the neuropathy patient described in this case. The patient should be advised to use “walking” glasses, which correct distance vision only, and have a separate pair of glasses to be used for reading.

Physical Training

In 20 older subjects with neuropathy who were randomized to a 3-week balance and ankle strengthening program or a 3-week sham exercise program, intervention subjects showed significant improvements in unipedal balance time, functional reach, and tandem stance. The trial was small and single blind so firm conclusions cannot be drawn; however, the exercises were well tolerated, and thus, are reasonable to consider for this type of patient. In addition, strengthening of the hip abductor/adductor groups and trunk musculature is intuitively appealing as a technique that may minimize excessive lateral trunk shift during gait. The author has seen clinical improvement in the gait of patients with neuropathy who have followed such programs. Finally, in a secondary analysis of gait data previously obtained, active ankle frontal plane range of motion (ROM) (i.e., ankle inversion/eversion) was a significant predictor of step-width variability and range during neuropathic gait on a smooth surface, independent of neuropathy severity. Therefore, although cause and effect were not confirmed by this work, the data suggest that increasing ankle eversion and inversion ROM may allow improved frontal plane control during neuropathic gait. Finally, strengthening of the UEs so that 25% to 30% of the patient’s body weight can be supported on a cane may be beneficial for reasons described below. A reasonable physical therapy program would include: strengthening of the ankles and hips with emphasis on muscles that control motion in the frontal plane (ankle invertors/evertors and hip ab/adductors), maximizing frontal plane ankle ROM, progressively more challenging balance and gait exercises and UE strengthening so as to support 25% to 30% of body weight with one limb.

External Devices

The ability of canes to improve balance has been confirmed in two separate protocols involving patients with neuropathy. In the first case, a cane was found to markedly improve the ability of older neuropathic subjects to maintain unipedal balance for 3 seconds when challenged with an inverting or evertting perturbation. Two findings were of clear clinical significance: (1) subjects performed equally well whether the perturbation was toward or away from the cane; and (2) up to 25% to 30% of a patient’s body weight was placed on the cane during this simulated emergent recovery of balance. In a separate study, 43 older neuropathic subjects underwent gait analysis on an irregular surface in low light conditions with and without three interventions: a cane, ankle orthoses, and touch of a vertical surface. The interventions were chosen to improve frontal plane control, given the injury potential of lateral falls. Step width variability and step time variability were chosen as outcomes, given work supporting the former as a marker of dynamic frontal plane control, and the association between the latter and falls. Each of the three interventions significantly decreased step width and step time variability, as compared to the baseline condition, and did so after the subject was given just 5 minutes of practice with each intervention. It seems likely that the interventions made the subjects more robust to perturbations during single stance which, in turn, allowed for a more controlled placement of the swing limb.
Accentuating Plantar Surface Sensation

Older persons with decreased plantar sensation demonstrated more rapid responses to frontal plane perturbations when standing on small (1 mm) ball bearings.\(^9\) In addition, a similar group of patients showed diminished standing sway when insoles provided vibratory noise to the plantar surface of the feet.\(^10\) The effect of these interventions on the gait of patients with neuropathy under standard and challenging conditions is not yet known.

UPPER EXTREMITY FUNCTION

If the patient describes difficulty with the performance of self care and typical domestic activities due to UE weakness, clumsiness, or loss of dexterity, then a referral to an occupational therapist is desirable. In addition to recommending specific exercises to maximize residual neuromuscular function, adaptive equipment to simplify specific tasks can be recommended and prescribed.

MINIMIZING LOSS OF FUNCTION IN THE EVENT OF A FALL

Despite everyone’s best efforts, the patient is still at increased risk for falling due to her age and gender. Evaluating and then optimizing bone density is the best way to minimize the risk of fracture and the accompanying loss of function, should the patient fall. However, even if the patient should fall and not be injured, the physician should consider the often intense psychologic trauma that results, and then provide reassurance and physical therapy as necessary to allow the patient to regain her previous level of function.

CASE DESCRIPTION REFERENCES


EVALUATION AND TREATMENT REFERENCES

REFERENCES


Neuromuscular Update II

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2008 COURSE F
AANEM 55th Annual Meeting
Providence, Rhode Island

Copyright © September 2008
American Association of Neuromuscular & Electrodiagnostic Medicine
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Printed by Johnson Printing Company, Inc.
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# Neuromuscular Update II

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### Objectives

The overall objective of this two-part neuromuscular update course is to present participants with clinical cases in neuromuscular diseases. At the end of the entire course, participants will learn how to diagnose, evaluate, and in some instances treat neuromuscular diseases. This course is an excellent review of neuromuscular medicine. Update II covers brachial plexopathy, painful small-fiber neuropathy, metabolic myopathy, and asymmetric motor weakness.

### Prerequisite

This course is designed as an educational opportunity for physicians.

### Accreditation Statement

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

### CME Credit

The AANEM designates this activity for a maximum of 3.25 AMA PRA Category 1 Credit(s). If purchased, the AANEM designates this activity for 2 AMA PRA Category 1 Credit(s). This educational event is approved as an Accredited Group Learning Activity under Section 1 of the Framework of Continuing Professional Development (CPD) options for the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada. Each physician should claim only those hours of credit he or she actually spent in the educational activity. **CME for this course is available 09/08 - 09/11.**
2007-2008 AANEM NEUROMUSCULAR UPDATE COURSE COMMITTEE

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CASE DESCRIPTION

A 63-year-old man awoke one morning feeling well, moved his neck and felt a “snap” in the back of his neck. He walked down the stairs and by the time he reached the bottom, severe pain was shooting from his shoulders down both arms into his fingers. The man had associated severe weakness of both hands and arms. He drove himself to a local emergency department, holding his hands on the bottom of the steering wheel because he was unable to raise them higher; he was sent home with morphine after being told he had a “pinched nerve”. The symptoms did not resolve. He complained of sharp, stabbing pains shooting down his arms from the shoulders, “like an electric fence”, as well as severe prickling, paresthesias, and cramps. The patient began his evaluation at the Mayo Clinic 2 days after his symptoms began. During the 3 weeks after symptom onset, he lost 17 pounds. After 3 weeks, the pain was somewhat improved, especially on the left, though it still kept him awake at night, but his weakness and paresthesias were unchanged.

The patient’s medical history was remarkable for Type 2 diabetes mellitus, coronary artery disease, hypertension, and hypercholesterolemia. His medications included aspirin, atorvastatin, lisinopril, venlafaxine, famotidine, and metformin. He was on disability from a prior back injury which left him with three herniated disks in his lumbosacral spine. His 57-year-old brother also had diabetes mellitus and painful feet; there was no other history of neuropathic symptoms in his family.

PATIENT EXAMINATION AND EVALUATION

On examination, the patient’s mentation and cranial nerve function were normal. He had severe weakness, both proximal and distal, and absent reflexes, in bilateral upper extremities (UEs), with dense loss of pinprick sensation over a right superficial radial nerve distribution. Normal strength, sensation, and deep tendon reflexes were noted in the lower extremities (LEs). His plantar responses were flexor. He did not have high arches or hammertoes. There were no cerebellar signs, and his gait and station were normal.

An evaluation included elevated fasting glucose at 304 mg/dL and hemoglobin A1c at 13.5%. He had normal or negative complete blood count (CBC), creatinine, sedimentation rate, serum protein electrophoresis and immunofixation, angiotensin-converting enzyme (ACE), antineutrophil cytoplasmic antibodies (ANCA), rheumatoid factor, antinuclear antibody (ANA), extractable nuclear antigens (ENA), syphilis and human immunodeficiency virus. Cerebrospinal fluid (CSF) analysis revealed elevated protein at 80 mg/dL and glucose of 108 mg/dL, with only one nucleated cell, no unique oligoclonal bands, a normal immunoglobulin G index, negative microbiology studies (including Lyme disease), and cytology.

Nerve conduction studies (NCSs) revealed low amplitude median sensory antidromic responses on the right (10 mV) and left (12 mV). Right radial sensory response was absent. Ulnar motor amplitudes were low (5.0 mV on right and 5.3 mV on left). Right ulnar sensory response was low amplitude (4 mV). Right peroneal
motor response was normal amplitude (4 mV) with normal distal latency (6.3 ms) and mildly slow conduction velocity (37 m/s). Right sural response was normal amplitude for age (2 mV) with a mildly prolonged distal latency (4.7 ms). Needle examination of the right upper limb revealed fibrillation potentials in the first dorsal interosseus (FDI), deltoid, biceps, infraspinatus, pronator teres, and triceps, with no activation in the deltoid and infraspinatus, and reduced recruitment in the FDI and biceps. On the left side, there were fibrillation potentials in the flexor pollicis longus (FPL) and pronator teres, with no activation of the FPL and reduced recruitment in the pronator teres; examination of the left biceps and deltoid was normal. Examination of cervical paraspinous muscles was normal. There were mildly long duration motor units (MUs) in the right anterior tibialis and medial gastrocnemius, with normal examination of the vastus lateralis. The findings were consistent with a subacute neurogenic process of the right and left brachial plexus in a patchy distribution, with more severe involvement of the right upper trunk and the left lower trunk/median nerve distribution. A mild sensorimotor peripheral neuropathy was also found. A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for patients presenting with brachial plexopathy is broad and should be considered thoroughly in the evaluation of each patient. In certain clinical settings, alternative disorders such as cervical root disease and primary shoulder pathology must be considered. Clues to the accurate diagnosis of brachial plexopathy may include time course, presence of associated diseases (e.g., diabetes mellitus, cancer), presence of trauma, presence of significant pain, and whether the disorder is unilateral or bilateral.

Neuralgic Amyotrophy

A common cause of brachial plexopathy is an inflammatory-immune mechanism with Parsonage-Turner syndrome, also known as neuralgic amyotrophy (NA). This is perhaps the most well-recognized cause. Beghi and colleagues surveyed medical records of patients in Rochester, Minnesota, and found an overall incidence rate of 1.64 cases per 100,000 population.\(^\text{1}\) MacDonald and colleagues found an incidence rate of 3 cases per 100,000 population in a group of London practices.\(^\text{11}\) Inflammatory-immune brachial plexopathy can present with severe pain, typically involving a shoulder girdle. This may occur in the context of a recent infection, immunizations, or even surgical procedures, which are believed to trigger a more widespread immune attack on nerves; however, frequently such a history cannot be elicited. Following a period of intense pain (often requiring the use of narcotics), a patient will typically develop weakness, which may be quite severe, along with areas of numbness. The pain will usually subside as weakness is developing. Weakness and sensory loss are often patchy in inflammatory-immune plexus lesions, and may be a clue to diagnosis. Some respiratory symptoms can also occur in the context of hemidiaphragm paralysis (which can be seen on a routine chest x-ray). The overall prognosis is good, with near-complete recovery of function in most patients, though it may take months to years before a good functional outcome is achieved. These cases are usually isolated, but have been known to recur in some cases.

A large study of the natural history of patients with brachial plexus neuropathy was carried out by Tsairis, Dyck, and Mulder, which characterized the clinical presentation as well as outcome of these patients.\(^\text{18}\) A total of 99 patients were reviewed in the study, only 1 of whom had a family history of brachial plexus neuropathy. A slight majority (54/99) had no history of illness, immunization, or toxin exposure in the month prior to symptom onset. If a preceding illness was reported, it was usually a respiratory infection, or what was described as a “flu-like illness”. Of interest however, eight patients did report a marked increase in strenuous activity shortly before the onset of their brachial plexopathy. For the vast majority of patients (95/99), severe pain, usually of sudden onset, was the first symptom, and lasted from a few hours to a few weeks. Most of the patients developed maximal weakness within 2 to 3 weeks after the onset of pain. The overall prognosis was good, but as noted, recovery was slow. After 1 year, 60% of the patients with primarily upper brachial plexus lesions reported they had returned to normal, whereas none of the patients with primarily lower plexus lesions reported a return to normal at 1 year. However, of the 84 patients with followup data, 67 had returned to normal by the time of their last examination.

Van Alfen and colleagues recently reported on 246 patients with either idiopathic or hereditary NA and reviewed their clinical information; data was collected prospectively on some patients, retrospectively in others.\(^\text{19}\) A mean age of onset of 41.3 years was found. Involvement beyond the brachial plexus was less common in the idiopathic group (17.3%, most commonly in the lumbar-sacral plexus or the phrenic nerve). Nearly all of the patients suffered severe pain that was exacerbated by movement or contact to the affected area, typically resulting in sleep disturbances. The mean time until onset of weakness was 13.6 days in men, and 8 days in women. Recurrent episodes occurred less frequently in the idiopathic group; however, 26.1% suffered at least one recurrence, with a median time interval of nearly 6 years to recurrence. CSF analysis was performed in few patients, and in those, a minority (n=4, 12.5%) had abnormalities believed to be related to their syndrome (elevated protein in two). NCS and electromyography (EMG) were abnormal in 96.3% of patients. Overall, outcomes in these patients were not as favorable as other studies have suggested. Of the patients with idiopathic brachial plexopathy who had 3 or more years of followup, 46.2% suffered from ongoing chronic pain; 69.4% had ongoing mild paresis, but only 2.8% were left with severe paresis. The authors reviewed outcomes of patients who had been treated with corticosteroids versus untreated patients and acknowledge the difficulty of interpreting such data since treatment involved different doses and durations. Overall, weakness was found to improve faster in treated patients (28.3%) versus (6.3%) untreated patients. This result was statistically significant. NCSs and EMG tend to show patchy involvement of the brachial plexus, and abnormalities that often extend proximally to the root level, manifesting with fibrillations and/or long duration MUs in cervi-
neural paraspinal muscles. Findings on magnetic resonance imaging (MRI) of the brachial plexus vary. It is not unusual to have these studies reported as normal, and findings, when they occur, can be subtle. Higher-resolution (e.g., 3 Tesla) MRI can be helpful in distinguishing these features. A retrospective study of radiologic findings in 26 patients with the diagnosis of Parsonage-Turner syndrome by clinical and/or electrophysiologic groups and an abnormal MRI found that the most common abnormalities identified were changes of edema and/or atrophy in the supraspinatus or infraspinatus muscles, consistent with denervation changes.14

A study of brachial plexus biopsy of four patients with progressive worsening brachial plexopathy revealed significant mononuclear perivascular inflammation in both the epineurium and endoneurium, without evidence of necrotizing vasculitis from nerves in the brachial plexus; these pathological findings are strongly supportive of the presumption of an inflammatory-immune pathogenesis of Parsonage-Turner syndrome.15 In 2001, Dyck and colleagues reviewed 12 nerve biopsies of distal arm nerves (usually superficial radial) and 8 nerve biopsies taken directly from the brachial plexus in patients with brachial plexopathy.4 Fiber loss (multifocal in half of the cases) and changes were found, suggestive of immune mechanisms and microvasculitis.4 The authors concluded that inflammation and neuropathic change can involve the plexus and the more distal peripheral nerves (PNs) in these attacks. Immune modulating agents such as methylprednisolone are often used in an attempt to speed recovery or limit functional deficit, but no large controlled study has been performed and the efficacy of these agents is uncertain.

**Diabetic Cervical Radiculoplexus Neuropathy**

Another important entity to consider is diabetic cervical radiculoplexus neuropathy. Patients with diabetes mellitus have long been known to be at risk for “diabetic amyotrophy”, or by the name preferred for its anatomical specificity: diabetic lumbosacral radiculoplexus neuropathy. A study of the clinical, electrophysiologic, and pathologic features of 33 patients with diabetic lumbosacral radiculoplexus neuropathy was performed by one of the authors.5 This disease process begins with severe pain, generally in the thigh, followed by both weakness and sensory loss. It is typically associated with Type 2 rather than Type 1 diabetes mellitus, and the glycemic control usually is good. Weight loss is common. Though the initial presentation is often segmental and unilateral, it ultimately involves the entire LE and in most patients in this series (32 of 33), it became bilateral (median time to bilaterality 3 months). Pathologic study of nerve in these patients showed findings diagnostic or highly suggestive of microvasculitis in half of the cases, with an abnormal degree of inflammation found in all cases. Of interest, while this study focused on an LE problem, one-third (n=11) of the patients were also found to have UE abnormalities, 8 were found to have UE mononeuropathies, and 3 had bilateral but asymptomatic cervical radiculoplexus neuropathies.5 The coexistence of these UE findings is suggestive of a common underlying mechanism and may also represent microvasculitis, but coexisting compression neuropathies could be responsible for some of these cases of UE involvement. In a series by Katz and colleagues, of their 60 patients (15%), 9 who presented with diabetic lumbosacral radiculoplexus neuropathy also had UE involvement; 5 had unilateral UE involvement, and 4 had bilateral asymmetric involvement.8 In most of these patients, arm deficits resolved after a matter of months. At this time, the best treatment for diabetic cervical radiculoplexus neuropathy remains unclear.

**Necrotizing Vasculitis**

Another inflammatory cause of brachial plexopathy is necrotizing vasculitis. This can either be systemic or nonsystemic necrotizing vasculitis. The nonsystemic necrotizing vasculitis is probably caused by a similar mechanism of microvasculitis as diabetic or nondiabetic cervical or lumbosacral radiculoplexus neuropathies (discussed above). In contrast, systemic vasculitis usually involves large epineurial vessels with fibrinoid necrosis. Patients with microvasculitis are more likely to present with a syndrome that involves the upper part of the plexus, whereas large vessel vasculitis more often presents as discrete mononeuropathies. Typically, patients will have prominent pain as well as weakness and numbness. They may have elevated sedimentation rates or other markers of systemic illness such as an elevated rheumatoid factor, positive ANAs, positive ANCAs, and positive ENAs, among others. In systemic vasculitis, patients may also have other organ system involvement such as pulmonary, gastrointestinal, kidney, sinus, and others. In general, a tissue biopsy will be needed to make a diagnosis of necrotizing vasculitis. Upper limb nerves that can be biopsied include the superficial radial nerve, the antebrachial cutaneous nerves, and others.

**PN Sarcoïdosis**

Rarely, PN sarcoïdosis (PNS) may present with prominent UE involvement. PNS is usually a sensory predominant syndrome, and is often a monophasic illness. Neurosarcoidosis will typically present subacutely. Clues to the presence of possible sarcoïdosis would include a history of sarcoïdosis, elevated ACE levels, and elevated calcium levels. Burns and colleagues studied the clinical, electrophysiological, and pathologic features of PNS in 57 patients.2 The most common neuropathic pattern is a polyradiculoneuropathy; almost half of the patients in this series had asymmetric involvement. While overall it is much more common to have LE predominance, 8/57 (14%) of their patients had UE greater than LE involvement. To make this diagnosis, a nerve biopsy or other tissue will generally be needed. Consequently, in an upper limb and sensory predominant syndrome, sarcoïdosis should be considered.

**Multifocal Inflammatory Demyelination**

Another inflammatory cause of a brachial plexopathy is multifocal inflammatory demyelination. The Lewis-Sumner syndrome, or multifocal chronic inflammatory demyelinating polyneuropathy, is a long-described entity that presents as an asymmetric neuropathy. However, even more focal involvement of the brachial plexus from inflammatory demyelination can occur and has recently become more recognizable.17 The NCSs may not show typical demyelinating changes since the lesions may be more proximal than
the sites where the nerve is studied, and focal conduction blocks and slowing may not be demonstrated. In such cases, proximal stimulation can be very useful. As opposed to typical chronic inflammatory demyelinating polyneuropathy (CIDP), which can usually be diagnosed without the need of nerve biopsy, focal CIDP may require biopsy for a firm diagnosis. Through the use of targeted fascicular biopsies taken at the sites of lesions on MRI (focal increased T2 signal, enlargement, or enhancement of a segment of nerve), many such cases have been diagnosed over the last several years. Nerve biopsy may show epineurial and endoneurial inflammation with demyelination and/or onion-bulbs. Often, these cases are predominantly motor and involve little pain. Correct diagnosis is very important in these cases as they are potentially treatable, and pathologic diagnosis, in particular, is helpful in ruling out other etiologies such as malignancies. Patients who have failed a treatment trial with an immunosuppressive drug or have a history or lesion that is worrisome for malignancy are frequently biopsied.

**Tumors**

Tumors can also cause brachial plexopathies. Clues to a mass lesion that is responsible for the plexopathy include a history of cancer, and the presence of Horner’s syndrome on the same side of the plexus lesion, which can suggest the extension of tumor into the area of the sympathetic chain. At times, a palpable lump may be observed in the supra- or infraclavicular area, which can sometimes induce shooting neuropathic pain when palpated. One of the more common groups of tumors that can cause brachial plexopathies are metastatic tumors. These include breast, lung, and lymphoma. The authors have personally seen many cases of breast cancer present with brachial plexopathy, often years after the original tumor. One important differentiation is brachial plexopathy caused by infiltrative tumor versus one caused by radiation injury. Radiation injury causing a brachial plexopathy is also quite common, frequently in the context of treatment for breast cancer. When the plexopathy is from tumors, it is often more painful. Plexopathies due to radiation injury frequently will show myokymia on EMG, but the presence of myokymia does not exclude metastatic tumor. Harper and colleagues studied patients with neoplastic brachial plexopathy and radiation plexopathy and found that 63% of patients with radiation plexopathy had myokymia on EMG, while only 2 of 55 patients with neoplastic plexopathy demonstrated myokymia on EMG, both with only brief myokymia in a single muscle. Overall, the most common muscles in which myokymia was found were the pronator teres and the abductor pollicis longus. Radiation plexopathy will often present many years after the initial radiation.

Another type of tumor that causes focal neuropathy, including brachial plexopathy, is perineurioma. Perineurioma is a benign tumor or malformation of perineurial cells that produces pseudo onion-bulb-like formations. They occur half the time in children and the other half in adults. They are very slowly progressive neuropathies. Although they tend to be motor predominant, most of them do have mild sensory involvement. Pain, especially severe pain, is atypical. MRI shows gradual enlargement of nerve fascicles (fusiform) without focal nerve tumors, and CSF analysis is generally normal. There is avid contrast enhancement. Perineuriomas do not need to be resected, but a diagnosis cannot be definitively made without a nerve biopsy. They differ from focal hypertrophic neuropathy (such as CIDP) in that they have pseudo onion-bulbs instead of true onion-bulbs. These pseudo onion-bulbs are made out of perineurial cells (which react to ENA) and not out of Schwann cells (as in true onion-bulbs). Neurofibromas and schwannomas can also cause brachial plexopathy. In the case of neurofibromas, one would expect other cutaneous manifestations of neurofibromatosis, such as café au lait spots, and axillary freckling. Malignant nerve sheath tumors can occur sporadically or in association with neurofibromatosis. Granulocytic sarcoma, a focal form of acute myogenous leukemia, has been reported to present as a brachial plexopathy. Clues to the presence of a malignant PN sheath tumor rather than a benign process include significant pain, and rapid progression of symptoms. The prognosis for this tumor is poor and often requires amputation of the affected limb.

**Other Considerations**

Other infiltrative conditions that cause brachial plexopathies include lymphoma and amyloidosis. Lymphoma can directly involve PNs. In only about half of the cases at Mayo Clinic, Rochester was the lymphoma recognized before it was found in PN. Features that should cause a physician to consider that lymphoma is the cause of the brachial plexopathy include severe pain, weight loss, constitutional symptoms (including night sweats and fever), and associated cranial neuropathies or other radiculopathies. CSF involvement with lymphoma cells is common, but repeated lumbar punctures may be necessary to obtain a positive cytology. A review of 23 patients with lymphomatous involvement by PN found that the most common clinical presentation was brachial plexopathy (n=7), followed by polyradiculoneuropathy. Another condition that can cause a brachial plexopathy is focal amyloid deposition. This focal amyloid deposition (often called amyloidoma) can certainly involve roots, plexus, or individual nerves, and while rare, should be considered; this often presents insidiously over years, but can produce focal neuropathies. Paraneoplastic syndromes can present as brachial plexopathies; in these syndromes, patients develop pain, weakness, and numbness in association with a malignancy but not due to direct tumor infiltration. They are likely the result of an immune mechanism. Similar immune-mediated brachial plexopathies can occur after surgery.

Vascular causes of brachial plexopathies also occur. Vascular malformations can occur in nerve, but are rare.

Other important causes of brachial plexopathy are trauma, stretch, compression, or surgical injury. There are many causes of trauma to the brachial plexus, with motor vehicle accidents a common inciting event. In these, it is important to try to separate avulsion injury from true brachial plexus injury. It is also important to separate those cases in which a nerve is transected (cases that may require nerve surgery) from those cases where the nerve is damaged but not transected (unlikely to require surgery). Stretch injury to the brachial plexus can occur with either an upward thrust of the arm over the head, or by a stretch of the neck away from the
shoulder; these can cause injury to an infant during delivery (Erb’s or Klumpke’s palsy). The prognosis is usually good in the non-transected nerve injuries, and physical therapy is helpful in their recovery. Although damage to the brachial plexus can occur by stretch or compression in normal nerve, it occurs more readily in entities in which the nerve is more susceptible to injury, such as hereditary neuropathy with liability to pressure palsies (HNPP). In this condition, the brachial plexus can be compressed by backpack straps over the shoulders, the improper use of crutches, and improper positioning during surgery. A more controversial cause of compressive injury is thoracic outlet syndrome; the putative etiology is compression of some part of the brachial plexus by a rib or fibrous band, leading to what is usually a lower plexus syndrome, which can be exacerbated by position. Various surgical procedures are considered, including rib or band resection as well as scalenectomy.

Hereditary cause of brachial plexopathy should also be considered. As previously mentioned, HNPP can lead to the development of a brachial plexopathy as well as mononeuropathies at common sites of compression. It is typical to have a superimposed mild peripheral neuropathy with this condition. This is often asymptomatic and is only found by electrophysiologic testing. Useful features in this diagnosis include a positive family history, and the presence of more than one compressive neuropathy or plexopathy, particularly in a different part of the body. Multiple mononeuropathies caused by vasculitis are much more likely to be associated with significant pain. Other hereditary considerations include neurofibromatosis (as described previously), and hereditary brachial plexus neuropathy. Attacks of brachial plexopathy can occur at any age, even in childhood. Patients with this entity will generally have multiple attacks of brachial plexopathy which are usually very painful. Like Parsonage-Turner syndrome, improvement in pain often coincides with development of weakness in the affected limb. Cranial nerve involvement can occur, as can lumbosacral plexus involvement, either simultaneous with or independent from, attacks of brachial plexopathy. There is generally good resolution between episodes. Family history and history of multiple attacks is helpful in making this diagnosis. However, it may not be possible to distinguish cases of hereditary brachial plexus neuropathy from typical Parsonage-Turner syndrome. Several dysmorphic features, such as hypotelorism, have been reported in these families, but the clinical significance of this is uncertain. Some families with this disorder have been found to have an abnormality at chromosome 17p25, 10,21 while other families have not. 20 There is clearly some genetic heterogeneity. CSF analysis may show elevated protein, but generally not a pleocytosis. NCSs and EMG are important, but it must be remembered that the findings are often patchy. MRI of the brachial plexus may be useful, but a negative study does not rule out this entity. A study by Klein and colleagues of four patients with hereditary brachial plexus neuropathy with UE nerve biopsy showed significant abnormalities in two of the four nerves studies. 9 The findings consisted of increased rate of axonal degeneration, and inflammatory infiltrates which involved and caused destruction of blood vessel walls (microvasculitis); necrotizing vasculitis was not observed. These findings suggest that despite the hereditary basis of the disease, the pathologic process may still be inflammatory-immune, and thus, potentially responsive to immunomodulatory therapy such as corticosteroids (as is suggested by improvement in pain with corticosteroid treatment of two patients in this study).

**STANDARD EVALUATION**

In the evaluation of patients with brachial plexopathy, a wide variety of conditions must be considered. Aggressive workup is required to determine the etiology of this potentially disabling condition. These studies generally include an MRI of the cervical spine as well as the brachial plexus. The brachial plexus MRI is particularly useful if a high resolution (3 Tesla) magnet and gadolinium are used. NCSs and EMG are essential for localization. NCSs of the superficial radial and the lateral and medial antibrachial cutaneous nerves, with comparison to the opposite side, can be particularly helpful. An extensive needle EMG examination may be required because the disease process is often patchy. A thermodiagnostic sweat test may show patchy sweat loss. Quantitative sensory testing can show the different classes of fibers involved, such as large myelinated fibers with vibration, small myelinated fibers with cooling, and unmyelinated fibers with heat-pain thresholds. A broad range of blood work should be considered, such as sedimentation rate, CBC, rheumatologic markers (e.g., rheumatoid factor, ANA, ENA, ANCA), ACE (looking for sarcoidosis), paraneoplastic antibody panel (looking for cancers), fasting blood sugar (looking for diabetes mellitus), hemoglobin A1C (looking for glucose dysregulation over the course of previous months), immunofixation (looking for monoclonal proteins such as could be seen in focal amyloid, lymphoma, or monoclonal gammopathy of undetermined significance - associated neuropathies), and spinal fluid evaluation (looking for abnormal protein, cell count, cytology). Occasionally, a bone-marrow biopsy (looking for a hematological malignancy or amyloid) is helpful. More specific evaluations should then be performed, depending on the evaluation results. Ultimately, to conclusively evaluate brachial plexopathies, a nerve biopsy may be required in some cases. With this approach, the underlying cause of brachial plexopathies can often be determined and the appropriate treatment initiated.

**CLINICAL AND ELECTRODIAGNOSTIC EVALUATION**

The most important diagnostic tool for the evaluation of a possible brachial plexopathy is a thorough and accurate history. The history must be accompanied by a solid understanding of the risk factors for development of brachial plexopathy. The most common etiologies of brachial plexopathy include trauma, surgery (e.g., related to arm positioning, injury with interscalene or axillary regional anesthetic block), birth injury, inherited genetic mutations (e.g., hereditary neuralgic amyotrophy), a primary autoimmune process (e.g., Parsonage-Turner, or NA), previous radiotherapy, and neoplastic invasion. 2,9,11 Systemic vasculitis and PNS are other uncommon etiologies. Diabetes mellitus is a risk factor for an immune-mediated brachial plexopathy (i.e., diabetic cervical radiculoplexus neuropathy secondary to microvasculitis). 1,5 Thus, if
a prior or concomitant history of any of these risk factors (e.g., previous surgery, trauma, family history, diabetes, etc.) is present, the clinician should strongly consider that etiology, yet still consider other plausible causes. It is also helpful to appreciate that recent infection, vaccination, and parturition are triggers for the immune-mediated plexopathies (e.g., hereditary NA and NA). There are often other clues in regards to etiology that are found in the symptomatology of the plexopathy. For example, the abrupt, spontaneous onset of shoulder UE symptoms favors an immune-mediated (e.g., microvasculitic) mechanism as seen with hereditary NA, NA, and diabetic cervical radiculoplexus neuropathy (CRPN), whereas a more gradual or insidious onset of symptoms would point towards neoplastic invasion or radiotherapy.

Other details about the course of symptoms and degree of pain are also important considerations. Immune-mediated plexopathies (e.g., NA) usually begin with severe pain, last days to weeks, and are followed by the development of weakness a few days to a few weeks later. Radiotherapy (e.g., for breast cancer) usually presents with much less pain than what is experienced by patients with plexopathy due to malignancy or to immune-mediated mechanism. Radiation-induced plexopathy usually presents more gradually and can occur months to decades after radiotherapy. Recurrent, painful brachial plexopathy is most typical of hereditary NA, whereas a more gradual or insidious onset of symptoms would point towards neoplastic invasion or radiotherapy.

In the patient previously described in the case presentation, the temporal evolution was of an abrupt onset neuropathic process that only gradually and incompletely resolved. The neuropathic process involved both UEs. The pain was so severe that the patient required narcotics. The patient had not experienced antecedent trauma, surgery, or radiotherapy. There was no family history of brachial plexopathy. These factors suggested that an immune-mediated plexopathy was very likely. Furthermore, the clinical setting was remarkable for diabetes mellitus and significant weight loss; diabetes mellitus is believed to be a risk factor for immune-mediated brachial plexopathy, and many of these patients experience contemporous weight loss. Thus, the most likely etiology for brachial plexopathy in this patient is diabetic CRPN. Additional evaluation, including examination and electrodiagnostic (EDX) testing, can be helpful in supporting this probable diagnosis.

CONSIDERING OTHER POSSIBLE ETIOLOGIES

In addition to considering etiologies for brachial plexopathy, the clinician needs to consider early in the work-up whether the process may simply be mimicking plexopathy and rather be caused by an alternative etiology. The presence of neuropathic pain can reasonably exclude from consideration pure motor processes that can affect the UEs, such as motor neuronopathies (e.g., amyotrophic lateral sclerosis), disorders of neuromuscular junction transmission (e.g., myasthenia gravis), and myopathies. Shoulder injuries can sometimes superficially mimic brachial plexopathy, but usually only when symptoms are relatively mild and before the examination and EDX testing identifies plexopathy. The most important mimic of brachial plexopathy is probably cervical radiculopathy or polyradiculopathy. These nerve root lesions also typically present with both weakness and pain. The pathomechanism of nerve root injury can be structural (e.g., neural foraminal stenosis or disk herniation), infectious (e.g., Lyme neuroborreliosis), or neoplastic (e.g., carcinomatous meningitis). In this case, infectious cervical polyradiculopathy is perhaps the most likely alternative etiology (other than plexopathy); EDX testing will prove helpful in excluding this possibility.

Localization

The history, neurologic examination, and EDX testing are very helpful in confirming and localizing a brachial plexopathy, but localization requires that the examiner have a reasonably good understanding of the neuroanatomy of the plexus. The brachial plexus is derived from the anterior primary rami of the C5 - T1 roots. After exiting the intervertebral foramen, the roots divide into ventral primary rami, which contribute to the plexus, and posterior primary rami, which innervate the paraspinal muscles of the neck. Several individual nerves (e.g., phrenic, long thoracic) branch directly off the roots prior to formation of the trunks. The roots otherwise converge to form three trunks—upper, middle, and lower—in the supraclavicular fossa at the lateral border of the anterior and medial scalene muscles. The plexus transitions from trunks to cords via divisions (anterior and posterior) just beneath the clavicle. Lesions involving roots or trunks occur in the supraclavicular portion of the plexus, whereas lesions involving the cords and terminal nerves occur in the infraclavicular portion. Supraclavicular plexopathies are more common than infraclavicular lesions. The lateral, medial, and posterior cords—named according to their anatomic relationship to the axillary artery—form below the clavicle in the proximal axilla and terminate in one or more nerves.

The neurologic examination should focus on identifying any motor, sensory, and reflex impairment referable to the different components of the plexus. A diminished or absent biceps reflex would be expected for a brachial plexopathy involving the upper trunk, for example. Weakness involving the hand and wrist would point towards lower trunk/medial cord involvement. In addition to localizing a lesion to particular trunks and cords, the examination can sometimes help determine whether lesions are preganglionic (e.g., root avulsion) or postganglionic (e.g., upper trunk plexopathy). Weakness of the rhomboid muscles (from C4 and C5 roots) and the serratus anterior muscle (from C5, C6, and C7 roots) would suggest involvement as proximal to the cervical root. As discussed later, needle EMG examination of these muscles and cervical paraspinal muscles will also be helpful in determining where the lesions are along the length of the nerve. In this case, both proximal and distal UE weakness was identified, and UE reflexes were absent, suggesting bilateral pan-plexopathy.

EDX testing helps confirm the diagnosis and localization of a suspected plexopathy. Rarely, non-neuropathic processes (e.g.,
rotator cuff tendinitis) can mimic brachial plexopathy, in which case EDX testing and the neurologic examination will be normal. More commonly, EDX testing serves to confirm localization of a neuropathic process to the plexus. A watershed for the localization of plexopathies is the dorsal root ganglia (DRG), with lesions involving segments proximal to the DRG (e.g., root) are classified as preganglionic lesions whereas those distal to the DRG (e.g., trunk) are labeled as postganglionic lesions. Assessment of sensory nerve action potentials (SNAPS) is very helpful with this localization because the preservation of SNAPs favors a preganglionic lesion (e.g., radiculopathy), while the diminution or loss of SNAPs favors a postganglionic lesion (e.g., plexopathy). For a unilateral plexopathy, the SNAP abnormality should be on the side of the lesion, and for asymmetric plexopathies, the SNAP abnormalities should theoretically be more severe on the more affected side. Side-to-side differences in SNAP amplitude of greater than 50% are typically considered significant, but repeat testing at the same setting to confirm that this finding is not simply technical is advisable, particularly given the significance of such a finding for localization. Differentiating preganglionic (e.g., radiculopathy) from postganglionic plexopathy is a particularly important request when trying to differentiate a structural (e.g., spinal stenosis), infectious (e.g., Lyme disease), or carcinomatous cervical polyradiculopathy from a plexopathy. Determining whether a traumatic plexus injury is preganglionic or postganglionic is also important for surgical management. For instance, preganglionic lesions (e.g., root avulsions) are generally not amenable to direct plexus repair with nerve grafting, and hence would more likely be surgically treated with a nerve transfer (e.g., spinal accessory nerve to suprascapular nerve in order to allow shoulder abduction, ulnar nerve fascicle to flexor carpi ulnaris to the musculocutaneous nerve in order to allow elbow flexion). On the other hand, postganglionic lesions (e.g., upper trunk plexopathy) may be directly repaired at the plexus with nerve grafting or internal neurolysis. Sensory NCSs for brachial plexopathy should include assessment of median, ulnar, radial sensory and lateral antebrachial cutaneous nerves. In this case, the low or absent median (bilateral), and ulnar and radial sensory responses, in the context of a sural sensory response that was normal for age, suggests that the clinically suspected brachial plexopathies are postganglionic (or at least not purely preganglionic).

Motor NCSs should be performed, particularly to look for low compound muscle action potential amplitudes over muscles innervated by affected nerves. Median and ulnar motor NCSs should always be performed; radial and musculocutaneous motor NCSs can sometimes be performed, but rarely provide critical information that can’t be obtained through the needle examination. In this case, the ulnar motor amplitude was low, whereas the peroneal motor amplitude was normal, consistent with the clinical impression of brachial plexopathy.

Needle EMG helps localize the lesion, both longitudinally (i.e., where along the length of the nerve or root), and specifically to components of the plexus (e.g., upper trunk). Needle EMG should ideally be performed at least 2 to 3 weeks after onset to maximize the data that can be collected from the study, but it still can be helpful to perform a study earlier than that because reduced recruit-
tions described as trialed in the same article include osmic acid and chloroform injections, as well as large doses of strychnine tonic.6

The treatment of a patient with a brachial plexus injury begins with exercises. The treating physician should prescribe that a patient be seen for occupational therapy (OT) or physical therapy. The patient should begin an exercise program to work on range of motion exercises, both during in-office therapy and at home on a daily basis. An exercise program for these patients is designed to keep the joints in a functional position, avoiding or treating contractures, while awaiting nerve recovery. For affected muscles that had active movement, the therapists instruct the patient in strengthening exercises to be gently performed as part of a daily exercise program.

The OT, or an orthotist, should provide bracing (orthoses) for any functionally significant joint deficits. The purpose of the orthosis is for protection and proper positioning of the joints, and/or to increase active function. In this case, the patient may benefit from a shoulder support on one or both sides for positioning, prevention of dislocation, and pain minimization. This has not been proven efficacious in brachial plexitis, but has been described as the standard of care in hemiplegic stroke.10 Wrist hand orthoses may be beneficial on both hands, either in a neoprene (wetsuit material), or polypropylene (hard plastic) style, depending on the degree of movement and level of discomfort present. A balanced forearm orthosis may be useful in this case for the right side in particular with its more severe proximal weakness. This allows movement of the upper arm, commonly to get the hand to the mouth to feed oneself. If the distal weakness is severe, orthoses are available to assist patients with activities of daily living (e.g., holding utensils, if the distal weakness is this severe, as well as to holding a pen, or using a toothbrush).

Pain management can also be addressed with the use of medications. Classic medications for neuropathic pain include tricyclic antidepressants (such as amitryptiline, taken at bedtime to assist with sleep), gabapentin or pregabalin (taken throughout the day), and antiepileptic drugs (including carbamazepine).5 Lidocaine patch 5% may assist with pain control as well.

Transcutaneous electrical stimulation (TENS) is frequently recommended for use of brachial plexus pain, with stimulation above and below the painful areas, with continuous low frequency current described, but not proven as beneficial.7 Melzak and Wall demonstrated that the effects of TENS are cumulative, with longer use more effective.8 It has also been described that 8 hours of use daily for at least 1 week should be trialed, then continued for at least 3 weeks if effective, with a taper off.4 TENS should not be used near a pacemaker, with someone who has a significant arrhythmia, nor over insensitive areas.7

Biofeedback and relaxation techniques have been advocated, but not proven efficacious in the treatment of painful brachial plexitis.5

Hopefully, treatment of the primary etiology, pain, and sleep deprivation will help resolve the issue of weight loss. If poor appetite becomes an issue, there are medications to assist with appetite stimulation.

Because of the expected recovery from the weakness and pain, in most cases, it will be necessary for the patient to have a temporary job adjustment or reassessment until the patient can return to previous work responsibilities.9

**CASE PRESENTATION AND DIFFERENTIAL DIAGNOSIS**

**REFERENCES**

2. Burns TM, Dyck PJ, Aksamit AJ. The natural history and long-term outcome of 57 limb sarcoidosis neuropathy cases. Journal of the Neurological Sciences 2006; 244: 77-87.

CLINICAL AND ELECTRODIAGNOSTIC EVALUATION REFERENCES

REHABILITATION AND TREATMENT REFERENCES
CASE DESCRIPTION

A 52-year-old woman presented with a chief complaint of numbness and pain in the feet. Symptoms became noticeable 2 years before and had been slowly progressive over time. The patient characterized the sensation as an underlying burning feeling with frequent but intermittent lancinating pain. These problems affected the feet symmetrically. Symptoms were constant but more bothersome with prolonged standing or walking and were worse at the end of the day, interfering with sleep. She described no muscle weakness or back pain. Although her strength was not affected, she admitted that because of pain, her activity level had diminished, she had gained weight, and she felt depressed about the change in her lifestyle. Her previous medical history was notable for hypercholesterolemia and mild and well-controlled hypothyroidism, for which she was taking simvastatin and levothyroxine, respectively. Simvastatin was started after symptoms began and did not result in any appreciable increase in symptom severity.

Examination

The patient was an overweight woman weighing 249 pounds. Examination of the cranial nerves and upper extremities was normal. In the legs, strength was normal. Patellar reflexes were normal, and Achilles reflexes were 1+ bilaterally. Pinprick sensation was diminished below the knees and in the fingertips. Vibratory and proprioceptive sensation was normal. Her gait was normal.

Prior Studies

Previous tests including comprehensive metabolic panel, complete blood count, C-reactive protein, erythrocyte sedimentation rate, antinuclear antibody, rheumatoid factor, vitamin B12, vitamin E, folate, rapid plasma reagin, thyroid stimulating hormone, and hemoglobin A1c were normal.

Current Studies

Nerve conduction studies (NCSs) and needle electromyography (EMG) were normal. Serum protein electrophoresis (SPEP), performed twice, showed mild polyclonal hypogammaglobulinemia but was normal on a separate occasion. Quantitative serum immunoglobulin measurements showed a mildly reduced IgG level of 669 mg/dL (normal 700-1600 mg/dL) and normal IgA and IgM levels. Immunofixation electrophoresis (IFE) was normal. A 24-hour urine protein electrophoresis (UPEP) was normal. Two hour oral glucose tolerance testing showed fasting glucose of 126 mg/dL and 2-hour glucose level of 256 mg/dL.

Differential Diagnosis

This patient had slowly progressive symptoms of both loss of nerve function (numbness) and abnormal positive neuropathic symptoms of burning and lancinating pain. In conjunction with mildly hypoactive Achilles reflexes on examination and loss of pinprick sensation in a symmetrical “stocking” distribution, her problem was most consistent with a distal sensory polyneuropathy (DSP) affecting small fiber more than large fiber modalities. Based on her early evaluation, this patient was initially considered to have mild idiopathic sensory polyneuropathy. The differential diagnosis in this situation is wide and should be considered in conjunction with more general causes of polyneuropathy, some of which may begin with a presentation of DSP and evolve to more extensive large fiber sensory and motor involvement.
Endocrine Disorders and Other Systemic Diseases

The single most common endocrine disturbance accounting for DSP is diabetes. Other endocrine disorders such as hypothyroidism, hyperthyroidism, and acromegaly are much less common causes of DSP. The association between diabetes and peripheral neuropathy has long been recognized. The most recent American Diabetes Association criteria define diabetes as fasting glucose ≥ 126 mg/dL or 2-hour glucose level ≥ 200 after a 75 gram oral glucose load. Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are defined respectively as glucose 100-125 mg/dL and 140-199 mg/dL. IFG and IGT may be seen separately or in combination and are likely due to predominant hepatic (IFG) or muscle (IGT) insulin resistance.19

In recent years, numerous studies have suggested that IFG and IGT may also be associated with neuropathy. In some series, 48% to 56% of patients with “idiopathic” or “cryptogenic” sensory predominant polyneuropathy were found to have some form of impaired glucose metabolism (IGM) when tested in detail.21,25,27 Others have found no clear association between IGM and sensory polyneuropathy.15 A clear relationship between IGM and sensory polyneuropathy remains to be proven, therefore studies are underway to examine this question.9 In this patient, the normal hemoglobin A1c suggested relatively mild diabetes but also suggested that a state of IGM or pre-diabetes was likely present for an unknown duration before its identification. In contrast, her hypothyroidism had been mild and well controlled with medication for at least 3 years prior to the onset of her neuropathy symptoms, making it a less likely contributor.

Other systemic diseases such as renal failure with uremia may cause a DSP, particularly if serum creatinine is 5 mg/dL or higher.5 Polyneuropathy in chronic hepatic failure is also common and may begin with a distal sensory predominant pattern. Primary biliary cirrhosis may be independently associated with a sensory polyneuropathy; distinctive cholesterol laden cells may be found within layers of perineurium, endoneurium, and epineurium. Xanthomas may also be seen. Based on normal screening electrolyte and metabolic studies, these conditions were not applicable in this patient.

Drugs and Toxins

Many drugs are implicated in the development of DSP; a few commonly encountered medications are listed in Table 1. The mechanisms of injury vary, but with a few exceptions which may be associated with “coasting” or limited progression of symptoms after drug discontinuance, most drug-related polyneuropathies stabilize after the drug is withdrawn. Some patients may experience improvement after drug withdrawal. In this case, the patient was not taking medications that are known to produce sensory polyneuropathy. She was taking simvastatin, which some studies have suggested may possibly contribute to neuropathy.6 However, the simvastatin was started after symptoms began, making it an unlikely cause for her problem.

### Table 1 Examples of common medications associated with distal sensory polyneuropathy

<table>
<thead>
<tr>
<th>Category</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial</td>
<td>metronidazole</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>amiodarone</td>
</tr>
<tr>
<td>Chemotherapeutic</td>
<td>cisplatin</td>
</tr>
<tr>
<td>Antitumor</td>
<td>paclitaxel</td>
</tr>
<tr>
<td>Antiepileptic</td>
<td>phenytoin</td>
</tr>
<tr>
<td>Anti-inflammation</td>
<td>colchicine</td>
</tr>
<tr>
<td>Immune modifying</td>
<td>tacrolimus</td>
</tr>
</tbody>
</table>

Nonprescription ingested substances such as pyridoxine (vitamin B6) and ethanol also are associated with sensory neuropathy. Pyridoxine doses as low as 100 to 300 mg/day may cause sensory neuropathy or neuronopathy. Ethanol is a well recognized cause of sensory polyneuropathy, both independently and in association with nutritional deficiencies. Length-dependent sensory loss and pain with associated distal axonopathy are common with chronic ethanol abuse.17 Arsenic or thallium intoxication are less common exposures that may lead to DSP. A detailed social history and inquiry into over-the-counter supplements used by the patient revealed no suspicious exposures.

### Nutritional Deficiencies

Deficiencies of B-complex vitamins including thiamine (vitamin B1), niacin (vitamin B3), vitamin B6, vitamin B12 may all cause DSP, though large fiber modalities are more often affected in most vitamin B complex deficiencies. Thiamine deficiency is especially common in alcoholic patients. Folate and vitamin E deficiencies are relatively unusual causes of DSP and are almost always seen in association with other neurological findings. This patient did not have underlying risk factors such as alcoholism, prior gastric surgery, malnutrition, or unusual diet to suggest these possibilities.

### Infections

In industrialized areas of the world, the main infectious considerations in the polyneuropathy evaluation include human immunodeficiency virus (HIV), hepatitis C, and Lyme disease. Leprosy and diphtheria, which may also initially appear as DSP, are uncommon in Europe and North America. HIV infection may be associated with DSP, especially with more severe and longstanding infection. This effect is independent of dideoxynucleoside treatment, which can cause DSP in some individuals. However, use of these medications and highly active antiretroviral therapy does not appear to be
an overall risk factor for the development of DSP, possibly because suppression of HIV infection and improved immunity counterbalance antiretroviral neurotoxicity.5,24 Polyneuropathy in hepatitis C is most often seen with cryoglobulinemia, but may also occur without cryoglobulinemia. Lyme disease related peripheral nervous system (PNS) disease typically presents as cranial neuropathy or polyradiculopathy rather than DSP, though a distal, symmetrical pattern of involvement has been reported.16 Evidence of infection with the Borrelia burgdorferi spirochete is essential to the diagnosis. This patient had no risk factors or laboratory results to suggest an infectious cause for her neuropathy.

Inflammatory and Immune Mediated Conditions

Many inflammatory and immune mediated conditions may cause DSP. These disorders may involve numerous organ systems or may be isolated to the peripheral nervous system. Systemic necrotizing vasculitic conditions such as Churg-Strauss syndrome, polyarteritis nodosa, and Wegener's granulomatosis, among others, characteristically cause multiple mononeuropathies, but occasionally, patients may have a more unusual distal symmetrical sensory presentation. Individuals with other connective tissue disorders such as systemic lupus erythematosus, rheumatoid arthritis, and scleroderma may more commonly demonstrate DSP, with scleroderma patients more frequently developing progressive motor nerve involvement and weakness. Sjögren syndrome is classically associated with a sensory neuropathy or neuronopathy, ranging from mild distal sensory loss, paresthesias, and dysesthesias, to disabling sensory loss with sensory ataxia and pseudoathetosis. Concomitant symptoms including xerophthalmia and xerostomia are usually present. Hypersensitivity vasculitides related to cryoglobulinemia, bacterial or viral infections, or drugs may also result in DSP.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) may occasionally present with predominantly sensory symptoms. Albuminocytological dissociation in the cerebrospinal fluid and demyelinating features on NCS help distinguish sensory CIDP from inflammatory sensory polyganglionopathy which demonstrates an axonal or neuronal pattern of injury on electrophysiology.

Monoclonal gammopathies that are not clearly associated with underlying multiple myeloma, macroglobulinemia, lymphoma, or other identifiable syndromes are classified as monoclonal gammopathies of uncertain significance (MGUS). The majority of patients have monoclonal IgM, which may bind to myelin associated glycoprotein in up to half of patients. The neuropathy associated with this condition is symmetrical with features of both sensory and motor nerve demyelination; sensory complaints often predominate in the early stages of disease. The exact role of the monoclonal proteins found in MGUS related neuropathy is uncertain, but in some cases, the antibodies may mediate an autoimmune response.

Other rare causes of distal symmetrical sensory polyneuropathy include sarcoidosis and isolated PNS vasculitis. These conditions most often present asymmetrically. In this patient, one SPEP showed a mild polyclonal hypogamma-globulinemia, which was not present on repeat testing. The immunofixation electrophoresis (IFE) and urine protein electrophoresis (UPEP) were normal. Inflammatory markers were unremarkable, making vasculitic or other inflammatory conditions unlikely.

Paraneoplastic

Peripheral neuropathy is a common occurrence in the setting of malignancies, often as a consequence of chemotherapy toxicity. Direct infiltration of nerves resulting in DSP is relatively rare but has been reported with lymphoma. Occasionally, the effects of tumors on peripheral nerves are exerted remotely.23 One of the best described syndromes is associated with small cell lung cancer and the anti-Hu antibody, an antineuronal nuclear antibody (ANNA-type 1). Symmetrical sensory loss, paresthesias, and pain, are characteristic and may begin before the identification of cancer in many cases. Anti-Hu antibodies have now been described in a wide variety of other carcinomas such as those involving breast, prostate, gastrointestinal tract, and thymus, among others. Other paraneoplastic antibodies which may present with a sensory polyneuropathy include anti-CV2, anti-amphiphysin, and less commonly, anti-Yo and anti-Ri. Sensory polyneuropathy in this setting often occurs in combination with other neurological signs such as encephalopathy, autonomic dysfunction, and muscle weakness, which may aid in the differential diagnosis of these patients. DSP without an identifiable autoantibody may also occur with malignancies, especially that of the lung and also among patients who have experienced significant weight loss.

In patients with multiple myeloma, a painful sensory polyneuropathy may develop related to amyloid protein deposits composed of insoluble fibrils of immunoglobulin light chains. As disease progresses, muscle weakness due to motor nerve involvement is common. Other associated signs such as macroglossia, autonomic dysfunction, renal insufficiency or nephrotic syndrome, or marked weight loss may aid in the diagnosis. This patient had no systemic symptoms, signs, or laboratory results suggesting underlying malignancy. The patient in this case, had never smoked and was current on her routine health maintenance testing that included mammography as well as cervical and gynecological cancer screening.

Genetic Conditions

A number of genetic conditions can result in DSP. Disorders such as Fabry’s disease and Tangier disease are rare and usually present in childhood. Other findings such as angiokeratomas in Fabry’s and extremely low levels of high density lipoprotein cholesterol in Tangier are characteristic. Adults with familial amyloidosis, most related to a transthyretin (TTR) mutation, may be more difficult to recognize. While the disease is dominantly inherited, the expression of peripheral neuropathy may be highly variable even among patients with the same mutation. Other organ system involvement, such as cardiac or renal dysfunction, may sometimes
be present at the time of neuropathy diagnosis. Pain, sensory loss, and eventual weakness beginning distally and moving proximally are characteristic. Autonomic fibers are commonly involved and lead to orthostatic hypotension and other manifestations of autonomic insufficiency.

Numerous other hereditary neuropathies with prominent sensory loss and pain such as hereditary sensory autonomic neuropathy (HSAN) are well described. Dominant inheritance is most common, and in type I, onset is often in early to mid adulthood. Patients with HSAN type I may have autonomic disturbances (e.g., hyperhidrosis), but the prominent sexual and gastrointestinal abnormalities characteristic of many TTR amyloid polyneuropathy variants are relatively uncommon. Also, in contrast to type II hereditary motor and sensory neuropathy (HMSN II) patients who typically have more prominent motor deficits, individuals with HSAN I have more prominent sensory symptoms, which may be severe enough to result in repetitive mutilation injuries, ulcerations, infections, and ultimately bony deformities and necrosis. This patient had no known family history of neuromuscular disease or peripheral neuropathy.

**Idiopathic**

Although it has been the focus of detailed evaluation, the cause of DSP may remain unknown in a significant number of affected individuals. Some studies have suggested that serial follow-up and evaluation may occasionally demonstrate an underlying etiology, but reversible causes are not often found. The course of disease in idiopathic DSP is usually relatively benign with minimal progression of symptoms over many years. Severe disability is uncommon, though a patient’s quality of life may be compromised due to chronic pain.

**EVALUATION AND TREATMENT OF SMALL FIBER NEUROPATHY**

Nerve fibers that are <7 μm in diameter are defined as small nerve fibers. They include the small myelinated (Aδ) fibers that carry the cold perception, cutaneous nociception, and autonomic function (preganglionic fibers); and the unmyelinated fibers (C fibers) that carry the warm perception, heat pain, and autonomic function (post ganglionic fibers).

**Symptoms**

Dysfunction of small fiber neuropathy (SFN) typically present as painful paresthesias that may or may not be stimulus dependent. The spontaneous or stimulus-independent paresthesias (continuous or intermittent) may be described variously as burning sensation (“feet on fire”), electric-shocks, sharp (“knife like, jabbing, pins and needles”), tingling, prickling, shooting-lancinating sensations, or aching in toes and feet. These symptoms may be mild to excruciatingly painful, are generally worse at night, and may worsen with walking. The stimulus-evoked pain, also called stimulus-dependent pain (stimuli may be mechanical, thermal or chemical), may occur in response to normally non-painful stimuli (allodynia) or increased pain in response to normally painful stimuli (hyperalgesia). Some patients may have additional or exclusive negative symptoms such as numbness, hypoalgesia, or hypesthesia. Although most patients present with a length-dependent distribution of symptoms (stocking), a few may have symptoms starting in the upper extremities, trunk, or face.

Autonomic symptoms in the form of decreased or increased sweating (heat intolerance), dry eyes, dry mouth, erectile dysfunction, urinary incontinence, stomach fullness, diarrhea, dizziness or light headedness upon standing, or visual blurriness may also be described.

**DIFFERENTIAL DIAGNOSES**

Various etiologies of SFN include: diabetes (including impaired glucose tolerance), amyloidosis, hereditary sensory neuropathy, Tangier disease, Fabry’s disease, HIV, toxic exposure or ingestion (drugs, toxins, supplements), cryoglobulinemia, nutritional deficiencies, and inflammatory neuropathies.

It is important to exclude mimickers of SFN and remember that foot pain is not synonymous with SFN. Some large fiber neuropathies may present as painful feet; several non-neuropathic conditions including plantar fasciitis, arthritis, bursitis, tendonitis; tarsal tunnel syndrome, Morton’s neuroma, and erythromelalgia may also present as foot pain. Even bilateral lumbar radiculopathy (from lumbar stenosis) may present as foot pain.

It is also important to note that not all patients with SFN will present with painful feet. Patients may present with tightness, coldness, numbness, or restless leg syndrome. SFN may present in a nonlength-dependent fashion affecting patchy areas of the body including the face or trunk, without first involving the feet. Finally, SFN may present as acute or subacute burning pain rather than the typical and chronically painful neuropathy.

**Testing in Patients With SFN**

Laboratory testing is designed to confirm the diagnosis and severity of SFN, exclude other possibilities, and establish the etiology for SFN.
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DIAGNOSTIC CONFIRMATION

The traditional tests for peripheral neuropathy, NCSs and EMG, are normal in SFN patients, unless there is associated large fiber neuropathy. There have been recent reports that even though the sural nerve may have a normal amplitude, more distal plantar nerves may show abnormalities in patients with SFN.

Specific tests for small fiber or autonomic function include: sympathetic skin response (SSR), quantitative sensory testing (QST), quantitative sudomotor axonal reflex test (QSART), thermo-regulatory sweat tests (TST), cardiovascular reflex testing, axonal flare response, and skin biopsy (measuring intraepidermal fiber density). 10, 11, 14, 22

SSR

SSR is a response secondary to change in sweat-related skin electrical potential elicited by various electrical or mechanical stimuli. The advantage of SSR is that it is widely available, inexpensive, can be performed on routine EMG machines, and it correlates with diabetic neuropathy (one study), but not SFN. The disadvantages of SSR are that SSR testing has low sensitivity (10% in one study) and low specificity. The response tends to habituate with repeated stimuli.

QST

QST can detect SFN by measuring detection of thermal hot or cold stimuli or heat pain by giving calibrated stimuli using either the method of limits or forced choice protocols. The advantages include its semi-quantitative nature and increased sensitivity (range 60% to 85%). The disadvantages of QST are that it requires patient cooperation, there is a broad range of normal values between machines, it includes central pathways, and technical factors need to be strictly controlled. The American Academy of Neurology (AAN) has given a Level C recommendation to this mode of testing.

QSART

QSART measures post ganglionic sympathetic sudomotor function. The stimulation of axons is achieved by ACh iontophoresis and the output measured by a sudorometer. The advantages of QSART are that it has fair sensitivity (60% to 80%), it is objective, reproducible, and specific to peripheral nerves. The disadvantages include the fact that the equipment is expensive and it is a somewhat time-consuming test.

TST

TST involves dusting an indicator powder on a patient that will turn purple when the patient sweats on being placed in a hot room. Although TST has high sensitivity (70% to 80%), its disadvantages are that it is not specific for the peripheral pathway, it is only semi-quantitative, it is messy, time-consuming, and it requires a special room.

Cardiovascular Tests

Cardiovascular tests including heart rate and blood pressure variability with Valsalva maneuver, heart rate variability with deep breathing, and tilt table testing are valuable tests in patients with autonomic neuropathy. In patients with SFN, up to 57% have been shown to have heart rate variation with Valsalva or with deep breathing.

Axon Reflex Flare Reaction

Axon reflex flare reaction is a simple bedside test. The clinician lightly scratches the foot area with a pin and inspects for immediate local reddening due to vasodilatation (secondary to the release of histamine), and the surrounding wheal and flare response. This may be a useful test for impairment of C-fibers although the sensitivity and specificity of this test is not known.

Skin Biopsy

Performing a punch biopsy (1 mm thick) of the skin and measuring intraepidermal nerve fibers with panaxonal marker PGP 9.5 by confocal microscopy or imaging software is considered one of the most sensitive tests for confirming the diagnosis of SFN even though it received only a level C recommendation from the AAN. Reduction in small fiber density in the epidermal layer, abnormal axonal swellings, and the distribution of abnormalities may be useful to confirm SFN especially in cases where the presentation is atypical or the examination is normal. The advantages of skin biopsy include the fact that it is simple to perform; multiple sites can be examined multiple times, and it has been shown to correlate with symptoms, signs, and nerve biopsy. Skin biopsy has been shown to correlate with QSART, electrophysiology, sural nerve morphometry, and the Gracely pain scale. In addition, it offers an important tool for longitudinal follow up of patients both clinically and for research purposes. The disadvantages of skin biopsy are the training and a large infrastructure needed to conduct this test. In addition, skin biopsy does not currently reveal any etiological information for SFN. In Figure 1, the left panel is normal skin from lower leg and the right panel demonstrates reduced intraepidermal fiber density from a patient with SFN.

Figure 1

Skin biopsy
Nerve Biopsy

Nerve biopsy may confirm the presence of SFN if electron microscopy is available to show the loss of unmyelinated fibers and proliferation of Schwann cell projections and regeneration. In addition, nerve biopsy may exclude large fiber sensory loss or the presence of inflammation and amyloid.

INVESTIGATING THE CAUSE

History of toxic exposure, medication usage, nutritional deficiencies, supplements (over the counter vitamins), alcohol abuse, and family history of neuropathy or diabetes are helpful clues in determining etiology.

The standard laboratory studies that may be useful in examining individual circumstances include: 2 hour oral glucose tolerance test (75 gm load), serum and urine immunofixation electrophoresis, HIV, antinuclear bodies, SSA, SSB, lip biopsy, transthyretin genetic testing, thiamine levels, galactosidase A levels, lipid panel, anti-Hu antibody, tissue transglutaminase, and nerve biopsy may be useful in individual circumstances.10,13

TREATMENT OF SFN

Attempts to treat painful SFN can be divided into those directed at treating the underlying etiology, and those directed toward symptom suppression based on neural mechanisms.

Even though painful neuropathies may not contribute to increased mortality, the pain may be so severe that it severely impairs the quality of life including normal work, activities of daily living, mood, and sleep. Treatment of neuropathic pain may improve the patients’ quality of life.

The first line therapy for neuropathic pain includes the tricyclic antidepressants and the antiepileptic drugs. The antidepressants include: the tricyclics (amitriptyline, nortriptyline, imipramine, desipramine, doxepin (10-150 mg qd), serotonin-noradrenaline reuptake inhibitors (NRIs): duloxetine (60-120 mg qd), and venlafaxine (150-225 mg qd). The antiepileptics include carbamazepine 100-800 mg qd, oxcarbazepine 1200-2400 mg qd, lamotrigine 200-400 mg qd, topiramate 300-400 mg qd, gabapentin 900-3600 mg qd, pregabalin 150-600 mg qd, and valproic acid 1000-1500 mg qd.

The second line therapies include the opiates: oxycodone 40-160 mg qd, morphine 90-360 mg po qd, Tramadol 50-400 mg qd, fentanyl patch 2-75 μg/hr q 2-3 days; the antiarrhythmics: mexiletine 600-1200 mg qd; topical treatments such as capsaicin 0.075% topical qid, lidocaine 5% patch, or isosorbide dinitrate spray 30 mg qhs. Other treatments to consider include clonidine 0.1-2.4 mg qd, memantine 55 mg qd, dextromethorphan 400 mg, levodopa 100 mg tid, alpha-lipoic acid (thioctic acid) 600 mg, spinal cord stimulators, transcutaneous electrical nerve stimulator units, and acupuncture.

Prognosis

Although there are no longitudinal studies of SFN patients the following four patterns are recognized:

Pattern 1: SFN progresses to involve the large fibers and patients develop the garden variety distal length-dependent sensory motor neuropathy.

Pattern 2: SFN progresses to more manifest involvement of autonomic fibers.

Pattern 3: SFN remains restricted to the small fibers.

Pattern 4: SFN symptoms resolve.

Patterns 3 and 4 are more likely to occur in patients with idopathic SFN.

REHABILITATION TREATMENT ISSUES IN SFN

Rehabilitation treatment concerns in regards to SFN deals primarily with pain symptom management issues. Pain associated with SFN can be severe and can have significant impact on mobility function and quality of life. Pharmacological treatment options may offer some relief from intense pain.

Currently, there are no specific guidelines on therapy regimen or therapeutic modalities to be used in SFN. The treatment plan may include a combination of medications, physical or occupational therapy, nerve blocks, and psychological interventions. Beyond the pharmacological treatment options, desensitization training by a therapist (physical therapy or occupational therapy), cognitive behavioral treatment by a psychologist specializing in pain management, meditation techniques, or acupuncture treatments are available.

Although no studies have specifically examined the role of desensitization training in patients with alldynia associated with SFN, studies suggest its potential role in complex regional pain syndrome (CRPS).2,28 Desensitization therapy comprises the essential therapeutic core element in the physical or occupational therapist’s management of alldynia in CRPS to restore functional use of the affected body parts. Somatosensory desensitization therapy for alldynia generally involves having the patient rub the affected body region over time with a series of progressively coarser and more irritating tactile stimuli. A treatment protocol may span 10 to 15 weeks, including home practice sessions and weekly clinic rechecks.2,29 The working mechanism of desensitization has not yet been established and the available research findings lack substantial efficacy data, as most involve case reports without the use of adequate control subjects.

Physical therapy approaches such as warm paraffin bath dips or cold soaks followed by massage may be utilized; however, patients should exercise caution due to a risk of impaired thermal and pain perception.

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sensitivity with SFN. In addition, prior to the use of either superficial mild heat or cold treatments, patients should be adequately educated and prepared for such trials as increased sensitivity to such modalities may occur with potential exacerbation of pain symptoms. Alternative treatment methods for neuropathic pain have not yet clearly demonstrated efficacy in studies. Yet, efficacy may vary depending on individual patients and the combination of treatment modalities used. Thus, a variety of different treatment options should be explored in consultation with individual patients. The general rehabilitation principles guiding the care of patients with SFN include preservation of function, minimizing complications, and improved quality of life while managing pain symptoms.

Pure SFN does not demonstrate significant muscle wasting, weakness, or reflex changes. However, some sensory or sensorimotor polyneuropathies are thought to begin with small fiber involvement and later evolve to affect large fibers. Therefore, within this context of evolutionary patterns of peripheral neuropathy, more advanced SFN may also display sensory numbness and motor weakness. Impaired pain and thermal sensitivity that accompanies SFN places the patients at great risk for developing foot ulcers, subsequent gangrene, and amputations. With concomitant sensory deficits and motor weakness, the medical care plan will need to include foot care and education, and appropriate orthotics as needed.

A more detailed discussion of orthotic and rehabilitation management of peripheral neuropathy in general is reviewed elsewhere. As a general rule, and in particular with SFN with its sensory impairments, prefabricated orthotics are not appropriate. Patients should be evaluated and fitted with custom-molded orthoses. A variety of orthotic options are available to meet the individual patient’s needs. The different orthotic options include: in-shoe inserts versus more extensive ankle foot orthoses (AFOs), ankle foot orthosis (with/without ankle joint articulation); different material (double metal upright versus thermoplastic); anterior versus posterior trimlines, dorsiflexion assist and stop; orthopedic shoes with wide toe box; rocker bottom shoes, and as necessary for ulcer healing, a total contact protected weight bearing orthosis such as total contact AFO or CROW (Charcot-Restraint Orthotic Walker).

REFERENCES


 CASE DESCRIPTION

An intelligent 24-year-old female patient documents her own medical history in a letter prior to her visit to Baylor College of Medicine as follows:

"I am seeking help in diagnosing a neuromuscular disease. I currently live in Virginia and I am moving back to Texas. I have had problems off and on since I was fifteen, but it seems that whatever it is might be getting worse and becoming a problem. I would like help diagnosing this or refer me to someone who would be more suited to helping me.

My first episode was when I was fifteen and I helped move a piece of furniture in my theatre class. My right forearm started to hurt, but by that night it had become rock hard and swelled. It had become painful to move and I went to the hospital emergency room. I was diagnosed with having compartments syndrome and was admitted overnight. The doctors had me sleep all night with my right arm in the air so that the swelling would go down. The next morning it was back to normal, and I went home.

Not until I was twenty-one did this happen again. My left forearm swelled up and had the symptoms as last time. I went to the ER and was given a muscle relaxer and sent home. Everything was back to normal again in the morning.

I have not had any major episodes since then until the ones I describe below. I have helped multiple times with moving heavy items and being out all day tailgating.

In May of this year, I attended a NASCAR race where I tailgated during the day and drank lots of water. When we walked to the track I could barely walk because my thighs were rock hard, and I had trouble bending my knees. During the race I began to feel light-headed and nauseous. I went down to the first aid center and was given four Motrin pills and told to drink water. Around midnight that night, I vomited and noticed my urine was the color of coke. This was on a Saturday night and on Sunday I went to a prime care facility where they performed a urinalysis. They were unsure of what was the problem. I spent that Sunday, Monday, and Tuesday barely able to urinate and vomiting. I couldn't eat or drink anything. They sent me to an internist on that Tuesday. He admitted me into the hospital for severe dehydration. I was seen by several doctors and was told that I had elevated creatine. I was also told I had rhabdomyolysis and acute renal failure. I was put on dialysis and constant fluids. I stayed in the hospital for a week and was then put on outpatient dialysis three times a week. I lost around 20 pounds within two weeks. I stayed on dialysis until the first of June. My kidney function had returned to normal, and I was told to take it easy.

On July 22, I lifted a small box of clothes that weighed around ten pounds. My left forearm started to swell and become hard. I was having trouble keeping the arm straight because of the pain.
Glycogen Storage Diseases

Patients with GSDs frequently develop symptoms during brief physical exertion of maximal intensity or sustained high intensity submaximal exercise due to the muscle's normal dependence on anaerobic glycolysis and carbohydrate oxidation. GSDs most often cause dynamic findings rather than static or fixed weakness. Some patients initially experience recurrent and reversible muscular symptoms that are exercise induced, but later develop fixed weakness in distributions mimicking acquired or hereditary myopathies. Table 1 includes a list of currently identified GSDs.

The most common GSD is myophosphorylase deficiency, also known as McArdle's disease or glycogenosis type V. Initial onset of symptoms often occurs during childhood and consists of poor endurance, fatigue, and exercise induced cramps and myalgia that mainly affects active muscle groups. Myoglobinuria may also be absent during childhood with the prevalence of fixed muscle weakness increasing as a patient ages. Symptoms can be precipitated by activities such as lifting heavy weights or climbing long flights of stairs. The "second wind" phenomenon is characteristic of this disorder. With the onset of myalgia, patients who rest briefly are then able to continue their physical activity with few or no symptoms. McArdle's disease is an autosomal recessive disorder with mutation in the gene that encodes muscle phosphorylase localized to chromosome 11q13. The normal function of muscle phosphorylase is to catalyze the removal of 1,4-glucosyl residues from glycogen to produce glucose-1-phosphate. Its absence leads to decreased metabolic substrate for glycolysis to produce adenosine triphosphate.

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<th>Glycogen Storage Disease</th>
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<td>Lysosomal Glycogenesis</td>
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<td>Acid maltase deficiency</td>
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<td>Lysosome associated membrane protein-2 deficiency</td>
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*Disorders in which exercise intolerance, cramps, and myoglobinuria are the most prominent presenting symptoms.

I decided to go to the hospital around ten o'clock that night due to what happened in May. I was also starting to lose sensation in my fingers and was experiencing shooting pains. They performed an ultrasound to see if I had any blood clots, which they did not find. They discovered that my CPK was off their charts. They told me their machine only went to 8000 and I was way over that. I was admitted into the hospital until my CPK went down so that I would not go into renal failure again. They also rigged my left arm into the air so that it could drain to avoid surgery since that had worked before. By Sunday morning my arm was somewhat better. I continued to have tingling and numbness in my fingers until about Monday or Tuesday. A neurologist, told me to follow-up with him after this episode had passed and my CPK came down. My CPK fell to around 2300 and I was released.

I saw the neurologist on August 15th and he has referred me down to Baylor since I am moving. He performed blood work and my CPK was around 600. He has told me that it is very important to get in with a neuromuscular specialist and let them start the work up.”

Upon her visit to the author’s clinic, further information was obtained. She had a history of hypothyroidism and what has been termed temporomandibular joint disorder due to her “jaw locking on occasion when chewing.” There was no family history of similar neuromuscular symptoms. Several members of the family had hypothyroidism. The review of other systems was entirely normal. A detailed examination revealed an only mild (5-/5) proximal weakness of upper and lower limbs. An electromyography (EMG) revealed short duration polyphasic units in the deltoids, iliopsoas, and left middle thoracic paraspinous muscles. There was no evidence of muscle membrane irritability. Serum creatine kinase (CK) was 1088 IU/L. Serum lactate, pyruvate and all other blood tests were normal.

What is the most likely diagnosis?

DIFFERENTIAL DIAGNOSIS

The constellation of symptoms consisting of exercise intolerance, muscle weakness, and myoglobinuria are most commonly associated with metabolic myopathies. These symptoms are the result of failure in energy production stemming from impaired lipid or glycogen metabolism, or mitochondrial dysfunction. The three main groups of metabolic myopathies are glycogen storage disease (GSD), fatty acid oxidation (FAO) defects, and mitochondrial cytopathies. Each group is clinically and genetically heterogeneous. The various disorders can have distinct neurological and systemic manifestations in addition to the muscular symptoms in different age groups. Furthermore, both transient and permanent muscle dysfunction can occur. Patients presenting with symptoms suggestive of these complex disorders can represent a diagnostic challenge for clinicians due to overlapping symptomatology among the various metabolic myopathies, as well as similarities to other acquired and genetic muscle diseases; however, a detailed patient history and laboratory testing can provide clues leading to the diagnosis.
CK is persistently elevated even between episodes of myoglobinuria. Electrodiagnostic (EDX) studies show normal nerve conduction studies. EMG is normal when patients are asymptomatic, but can show myotonic discharge and fibrillation potentials during an acute attack. Diagnosis can be made by demonstrating the absence of myophosphorylase on the muscle biopsy or genetic mutation analysis.

The myopathic variant of phosphofructokinase (PFK) deficiency (glycogenosis type VII) is similar to myophosphorylase deficiency in that patients experience exercise intolerance, cramps, and myoglobinuria. It is caused by a defect in phosphofructokinase b kinase, a key regulator of glycogen metabolism. PFK deficiency can be transmitted as an X-linked or autosomal recessive disorder. Phosphofructokinase (PFK) deficiency (glycogenosis type VII) is clinically indistinguishable from myophosphorylase deficiency. The main clinical features include exercise intolerance, myalgia, cramps, and exercise induced myoglobinuria. Despite the similarities, PFK can be differentiated from McArdle’s disease by routine laboratory testing. PFK is a tetrameric enzyme encoded by different combinations of three subunits located on separate chromosomal loci. The muscle (M) subunit is on chromosome 1, liver (L) subunit is on chromosome 21, and platelet subunit is on chromosome 10. The muscle expresses only the M isoform and erythrocytes express both M and L isoforms. A complete absence of the M isoform results in partial PFK deficiency in erythrocytes, causing hemolytic anemia. This is reflected in laboratory studies as elevated reticulocyte count and hyperbilirubinemia. Other clues for PFK deficiency include the presence of polyglucosan, in addition to glycogen deposits on the muscle biopsy. Polyglucosan stains intensely with periodic acid-Schiff reaction, but is resistant to diastase. PFK deficiency, like McArdle’s disease, causes impaired glycolysis, but the metabolic block is in the downstream glycolytic pathway. PFK deficient muscle cannot utilize glucose, and high carbohydrate meals exacerbate the exercise intolerance resulting in the “out of wind” phenomenon.

Phosphoglycerate kinase (PGK) deficiency (glycogenosis type IX) causes exercise intolerance and myoglobinuria. In addition, patients may have central nervous system dysfunction such as mental retardation, seizure, and hemolytic anemia. PGK deficiency also distinguishes itself as an X-linked disorder. The primary manifestation of phosphoglycerate mutase deficiency (glycogenosis type X) is exercise intolerance, exertion induced myalgia, cramp, and myoglobinuria. It is an autosomal recessive condition. Lactate dehydrogenase (LDH) deficiency (glycogenosis type XI) is a rare cause of exercise intolerance and myoglobinuria. It is due to mutation in the muscle specific subunit localized to chromosome 11. Patients have myoglobinuria, elevated serum CK, but low LDH.

Debrancher enzyme deficiency (glycogenosis type III) represents 25% of all GSDs. In the IIIa subtype, branching enzymes are absent in both muscle and liver. The most common presentation is childhood onset of liver dysfunction, hepatomegaly, failure to thrive, delay in motor skills development, and fasting hypoglycemia that resolves by puberty. Subsequent static weakness in the distal more than proximal muscles occurs during the third and fourth decade of life. Cases with exercise intolerance have been reported. Debrancher enzyme deficiency IIIa is an autosomal recessive disorder and the gene is localized to chromosome 1p21. EDX testing can be normal or reveal mixed myopathic and neurogenic features that suggest a neurogenic contribution to phenotype. The type IIIb form of debrancher enzyme deficiency does not have muscular manifestations.

Other GSDs including branch enzyme deficiency (glycogenosis type IV) and acid maltase deficiency (glycogenosis type II) typically cause progressive and static muscular symptoms. Exercise intolerance and activity induced symptoms are not prominent features in these disorders. In addition to the myopathic findings, other neurological or systemic conditions are frequently present.

**Disorders of FAO**

Myopathic symptoms such as myalgias, muscle fatigue, weakness, and myoglobinuria are most commonly induced by prolonged physical exertion in patients with FAO defects. This is due to the dependence of the muscle on stored lipid as the metabolite for energy production during long endurance activities. In addition to sustained activity, patients with this group of disorders frequently have muscular symptoms precipitated by prolonged fasting, infection, general anesthesia, and states of metabolic stress. The exact trigger for myopathic symptoms is sometimes unknown. Unlike adults, infants and young children with FAO defects have systemic involvement including hepatic dysfunction, cardiomyopathy, hypoketotic hypoglycemia, and generalized metabolic perturbation which can overshadow the myopathic symptoms.

Carnitine palmitoyltransferase (CPT) 2 deficiency is the most common cause of recurrent myoglobinuria in adults. The adult onset myopathic form of CPT2 deficiency typically manifests as recurrent paroxysmal myoglobinuria, muscle aches, and stiffness induced by sustained exercise. The myopathic attacks can also be triggered by febrile illness, prolonged fasting, cold temperature, or emotional stress. The precipitant is not identified in 20% of cases. The “second wind” phenomenon is not a feature of this disorder, and patients are able to participate in brief strenuous physical activities. Significant involvement of other organ systems is not characteristic of this disorder. Between episodes of myoglobinuria, patients with CPT2 deficiency are essentially normal, and the development of fixed muscle weakness is uncommon. Men appear to be more affected than women.

CPT2 deficiency is an autosomal recessive disorder, and the causative gene is localized to chromosome 1p32. Diminished CPT2 activity results in failure to transport long-chain fatty acids across the mitochondrial membrane into the matrix where FAO takes place. This ultimately leads to impaired energy production. Rare cases of clinically affected heterozygote with partial CPT2 deficiency have been reported. Routine laboratory studies between myopathic attacks may be normal or show elevated serum CK. EDX testing reveals normal nerve conduction studies and low-amplitude short duration motor unit action potentials on EMG. Routine histochemical studies of the muscle biopsy including sections evaluating glycogen and lipid content in an asymptomatic individual may be normal. The diagnosis can be made by demonstrating reduced CPT2 enzyme activity from the muscle specimen or fibroblast culture.
Childhood onset of hypoketotic hypoglycemia and multiple metabolic disturbances is the most common presentation for acyl-CoA dehydrogenase deficiencies. Recurrent myoglobinuria triggered by exercise or fasting is an uncommon phenotype of very long chain acyl-CoA dehydrogenase (VLCAD) deficiency. Isolated muscle involvement tends to have a later onset when compared to patients with generalized metabolic derangement. VLCAD deficiency is an autosomal recessive disorder caused by mutation in the gene ACADVL mapped to chromosome 17p13. Other rare cases of exertion-related myoglobinuria and episodic weakness with rhabdomyolysis have been described in medium chain acyl-CoA dehydrogenase (MCAD) deficiency and long chain acyl-CoA dehydrogenase (LCAD) deficiency. MCAD is localized to chromosome 1p31, and LCAD is mapped to chromosome 2q34. Recurrent episodes of exertion-induced myoglobinuria associated with a sensorimotor polyneuropathy have been described as an uncommon phenotype of mitochondrial trifunctional protein (MTP) deficiency. MTP is a multimeric enzyme with four α-subunits and four β-subunits. The α-subunits have long-chain 2-enoyl-CoA hydratase and long-chain L-3-hydroxyacyl-CoA dehydrogenase activities. The genes that encode α- and β-subunits are both localized to chromosome 2p23.

Mitochondrial Cytopathy

Mitochondrial cytopathy represents one of the most complex groups of disorders. Although the human mitochondrial genome is only 16.5 kb and encodes 13 structural proteins, many different clinical syndromes can result from mutations in these genes. The complexity of mitochondrial disorders stems from three unique features of mitochondrial genetics. First, all mitochondria and mitochondrial deoxyribonucleic acid (DNA) are derived from the oocyte. Second, mitochondria with different DNA sequences can coexist in a cell or tissue in a phenomenon known as heteroplasmy. When all of the mitochondrial DNA in a cell or tissue is the same sequence, it is known as homoplasmy. Heteroplasmy is important in mitochondrial disorders because mutant mitochondrial DNA can be present in different proportions in various cell populations. The pathogenic effect of the mutation will only be manifested when a critical level of mutant mitochondrial DNA is reached. This is known as the threshold effect. Third, mutant and normal mitochondrial DNA segregate randomly during cell division, thus changing the proportion of mutant DNA in the different cells over time.

Although exercise intolerance, myalgia, and recurrent myoglobinuria can be symptoms of mitochondrial disorders, the myopathic symptoms may occur in isolation or coexist with other neurologic and systemic conditions. Progressive fixed muscle weakness can develop in addition to the paroxysmal muscular symptoms. The genetic mutations responsible for myopathies can also cause multisystemic disorders.

EVALUATION

The possible causes of exercise intolerance and myoglobinuria are extensive. To determine the specific diagnosis, a detailed developmental and family history is critical in combination with a careful review of the circumstances and provocative factors associated with the patient’s muscular symptoms. Extensive laboratory testing, EDX evaluation, muscle biopsy with biochemical studies, and genetic mutation analysis may all be necessary before an exact diagnosis can be established. Despite an exhaustive effort, the underlying etiology may still elude even the most assiduous clinician.

TREATMENT

Currently, there is no effective cure for any of the metabolic myopathies. Lifestyle modification such as endurance training may improve exercise capacity in some patients with GSD. A regimen of moderate aerobic exercise can be tolerated by patients with McArdle’s disease without adverse muscle symptoms or elevation in serum CK. The improvement in oxidative and work capacity with physical conditioning may be due to increased mitochondrial enzyme level and cardiac output. Ingestion of sucrose prior to physical exercise can also increase exercise tolerance in patients with McArdle’s disease. Patients with FAO disorders and mitochondrial cytopathies are encouraged to avoid fasting and exercise during fasting or acute illnesses. Dietary changes and supplements have not produced sustained long-term functional improvement. Patients who have FAO disorders should avoid prolonged sustained exercise. Enzyme replacement therapy and gene therapy are among the potential innovative therapeutic options that may revolutionize treatment for these disorders.

REHABILITATION TREATMENT ISSUES IN MCARDLE’S DISEASE

McArdle’s disease (GSD type V) results from the absence of the muscle glycolytic enzyme, myophosphorylase. This enzyme deficiency leads to a muscle’s inability to break down glycogen for energy generation during anaerobic metabolism. In addition, a lack of myophosphorylase also impacts energy generation during aerobic metabolism due to decreased substrate generation (pyruvate) for the citric acid cycle. Glycogen is the most important source of energy for the muscle during early exercise and at high exercise intensities. The decrease in oxidative capacity of McArdle’s disease muscle is at less than half of normal muscle in the first few minutes of moderate exercise. More vigorous activity will trigger muscle cramps, pain, and myoglobinuria. Therefore, the blockade of glycogen breakdown in muscle results in a complex clinical pattern of exertional intolerance, muscle cramps, myalgia, second wind phenomenon, rhabdomyolysis, and myoglobinuria, as seen in McArdle’s disease.

Due to the risk for severe and potentially dangerous rhabdomyolysis associated with exercise, many patients with McArdle’s disease have traditionally been advised to avoid exercise. However, sedentary and inactive lifestyles for these patients results in deconditioning, which can further complicate and worsen the disease by decreasing cardiovascular and circulatory capacity. With deconditioning and decline in circulatory capacity, the
delivery of much needed bloodstream energy fuels such as glucose and free fatty acids to muscle becomes impaired in a clinical scenario where muscle energy imbalance is already compromised by the inborn error of glycogen breakdown. Research has also shown that deconditioning reduces levels of muscle mitochondria and mitochondrial enzymes that are necessary for metabolizing energy sources. Thus, avoidance of physical activity and adoption of an inactive lifestyle in McArdle’s disease patients for fear of muscle injury may result in a downward spiral of decreased exercise tolerance and aerobic capacity. In turn, this further lowers the threshold of physical activity, producing muscle injury and cramps.

Given these issues, recent studies have examined whether exercise training and aerobic conditioning can help ameliorate the symptoms of McArdle’s disease. Haller and colleagues have demonstrated the beneficial effects of a moderate intensity aerobic exercise program in improving average work capacity (36%), oxygen uptake (14%), cardiac output (15%), and citrate synthase and beta-hydroxyacyl coenzyme A dehydrogenase enzyme levels (80% and 62%, respectively) without causing pain, cramping, or increasing serum CK levels. The exercise regimen entailed cycle ergometry for 30-40 minutes per day, 4 days per week for 14 weeks, at an intensity of approximately 60% to 70% maximal heart rate. The investigators found that moderate aerobic exercise is well tolerated and when performed regularly, leads to adaptations that substantially increase oxidative and work capacity in patients with McArdle’s disease. A favorable response was also noted in a similar but longer (8 month) exercise training program study. Other case reports and studies also support the benefit of a moderate intensity aerobic exercise and activity program in patients with McArdle’s disease to improve exercise tolerance, work capacity, and overall health status. The beneficial effects of the exercise program are thought to occur through increasing cardiovascular fitness and improving circulatory delivery capacity, as well as increased mitochondrial enzyme level and improved metabolic efficiency.

Researchers have shown that ingestion of sucrose prior to an exercise program improves work capacity and exercise tolerance in patients with McArdle’s disease. It appears that smaller amounts (30 to 37 grams) of sucrose just prior to an exercise session may be as effective as a large amount (75 grams) ingested 30 to 40 minutes before exercise. It should be cautioned that when used regularly and in large amounts well in-advance of planned activities, sucrose ingestion may result in unintended side effects of weight gain and a potential for diabetes.

A recent Cochrane Review on pharmacological and nutritional treatment for McArdle’s disease concluded that there is no evidence of significant benefit from any specific nutritional or pharmacological treatment in McArdle’s disease. There is a lack of evidence to show benefit from supplementation with branched chain amino acids, depot glucagon, dantrolene sodium, verapamil, vitamin B12, high-dose oral D-ribose, or high-dose creatine. Low-dose creatine conferred a modest benefit on ischemic exercise testing, while high-dose creatine was found to worsen symptoms. A diet rich in carbohydrates may be better than a protein rich diet. Recent research has indicated that the severity of exercise intolerance correlates with insertion/deletion polymorphic variants of angiotensin-converting enzyme (ACE). Ramipril 2.5 mg orally daily showed possible benefit in McArdle’s disease patients with the D/D ACE haplotype.

Currently, there is no specific guideline for a physical therapy or an exercise program. A reasonable approach may be to discuss with the patient current knowledge in regards to exercise, sucrose, nutrition, and pharmacological treatment options in McArdle’s disease. A moderate aerobic exercise program with or without pre-exercise oral sucrose can be recommended. If the patient would like to pursue an exercise program, several things should be considered to provide the patient with the best chance for success. It is recommended that a structured exercise program be designed in a consultation with an experienced physical therapist who will be monitoring the patient and will be in contact with the physician. The exercise regimen should be an aerobic program, preferably either walking/treadmill or stationary cycle program, starting at low intensity (30% to 40%) during warm up period (5 to 15 minutes) with gradual progression to a goal of 60% to 70% maximal heart rate. Isometric, maximal effort, and high-weight, low-repetition exercises are to be avoided and listed under precautions for exercise prescription. Exercise duration should be about 30 to 40 minutes per day, and 4 to 5 days per week. Initially, heart rate and perceived exertional effort should be monitored and recorded. The physical therapist can instruct the patient in heart rate monitoring as well as provide feedback about concordance with perceived exertional effort. This will prepare the patient for transition to a self-monitored, home-based, long-term exercise program. If appropriate on clinical grounds, a sports drink containing 30 grams of oral sucrose just prior to the exercise session can be administered as a preventative measure for muscle cramps and exercise-induced myoglobinuria, especially during the first 5 to 10 minutes of the exercise program.

**BIBLIOGRAPHY**

7. DiMauro S, Andreu AL. Mutations in mtDNA: are we scraping the bottom of the barrel? Brain Pathol. 2000 Jul;10(3):431-41
Metabolic Myopathy


REHABILITATION TREATMENT REFERENCES


Progressive Asymmetrical Weakness

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CASE DESCRIPTION
A previously healthy 50-year-old man began to develop difficulty arising from a chair and climbing stairs. By the time of his first neuromuscular evaluation at age 54, he needed both arms to lift himself from a chair, both arms to pull himself up the stairs, and both hands to open a car door. He denied symptoms of myelopathy. The patient described some degree of numbness over digits 4 and 5 of the left hand. He occasionally had difficulty clearing his throat, and on questioning, described occasional coughing on particulate or dry foods.

At age 54, on motor examination of the upper body, neck flexion was graded 4/5, shoulder abduction 4.5/5, arm external rotation 4.5-4.8/5, elbow extension 4.5-4.8/5, and elbow flexion 3/5 on the right, 2.5-3/5 on the left. Wrist flexors and extensors were graded 4/5, with left wrist extension 3.5/5. Ulnar intrinsic hand muscles were graded 4.5/5 on the right and 3/5 on the left. Distal and proximal finger flexion was graded 3.5/5 on the right and 3/5 on the left, as was left thumb flexion, while thumb abduction was 4-4.5/5. In the legs, hip abduction, adduction, flexion, and extension, and knee flexion were graded 4/5. Knee extension was graded less than 2/5 on the right and 2/5 on the left. Foot dorsiflexion was graded 4/5 on the right and 2/5 on the left. Foot inversion and eversion were grade 4/5 and plantar flexion was 3/5, somewhat worse on the left. Muscle stretch reflexes were zero to trace throughout. There was marked thinning of musculature in the forearms, somewhat more prominent in the flexor compartment, and there was atrophy of ulnar intrinsic hand muscles, more prominent on the left. In the legs, there was prominent atrophy of the quadriceps muscle groups. Fasciculation and percussion myotonia were absent. No definite sensory deficits could be identified.

Electrodiagnostic Studies
The results of the nerve conduction studies (NCSs) for the upper and lower extremities can be found in Table 1. The needle electromyography (EMG) results are located in Table 2.

DIFFERENTIAL DIAGNOSIS
In summary, the patient presented with slowly progressive, painless muscle weakness. He had predominantly distal weakness in the arms (sparing of the shoulder girdle and triceps but involvement of the wrist and finger flexors and extensors), but proximal and distal weakness in the legs (involvement of hip girdle, knee extensors, and ankle dorsiflexion and plantar flexion). There was also asymmetry in muscle strength, particularly distally. Sensory examination was normal but he did have mild symptoms in the distribution of the left ulnar nerve. Muscle stretch reflexes were normal and plantar responses were normal.

In approaching patients with neuromuscular problems, the three main goals include localizing the site of the lesion, identifying the cause of the disorder, and successfully treating the patient.

The last goal is the most important to the patient and should be considered in determining how aggressively to pursue a work-up to identify the exact etiology of a disorder. For example, the physician may be able to make a diagnosis of Charcot-Marie-Tooth (CMT) Type 1 on clinical examination and electrodiagnostic (EDX) testing and could order genetic testing to see if there is CMT1A, IB, 1C, etc., but this may not be important to a patient, especially if they have to bear some of the costs and find that there is no specific
treatment for any of the subtypes. Make certain this is discussed with a patient before such tests are ordered.

The key to localizing the lesion is to assess the pattern of involvement and perform confirmatory EDX testing and laboratory evaluation. In the process, the exact diagnosis may be made or additional testing such as a muscle or nerve biopsy, genetic testing, or serological studies can be ordered.

In the patient presenting with asymmetric, predominantly motor weakness, affecting distal greater than proximal muscles in the arms and legs, the following disorders need to be considered:

- **anterior horn cell**
  - motor neuron disease (i.e., amyotrophic lateral sclerosis [ALS], spinal muscular atrophy, and poliomyelitis)
- **polyradiculopathies**
  - cervical and lumbosacral, syrinx, tumors of cord, Lyme disease, sarcoidosis, and tumor infiltration
- **plexopathies**
- **peripheral nerve**
  - CMT, multifocal motor neuropathy (MMN) and multifocal acquired demyelinating sensory and motor neuropathy, vasculitis, cancer, and amyloidosis, toxic/metabolic/endocrine
- **neuromuscular junction**
  - rare cases of myasthenia gravis (MG)
- **muscle**
  - distal myopathies/ muscular dystrophies, myofibrillar myopathy, glycogen storage diseases (e.g., acid maltase, debrancher, branching enzyme, phosphorylase kinase deficiencies), amyloidosis, polymyositis/dermatomyositis (rare), sarcoidosis/granulomatous myositis, and inclusion body myositis (IBM).

The lack of sensory abnormalities on examination or any sensory symptoms (except for the possible left ulnar distribution numbness), makes a polyradiculopathy/plexopathy or peripheral neuropathy less likely. The pattern of weakness was diffuse in this patient and not in the distribution of individual nerves, so it would seem that MMN is unlikely. About 5% of myasthenics will have predominately distal weakness but most patients have ocular involvement of some type (ptosis, blurred or double vision) and fluctuations in their weakness that the patient did not exhibit. Furthermore, because profound atrophy is not usually seen in MG as seen in this patient, MG does not seem likely in this case.

On the basis of the history and clinical examination, it is suspected that the patient has either an anterior horn cell disease or myopathy. In regards to motor neuron (MN) disease, there was no history of an acute febrile illness to suggest poliomyelitis (plus the progressive nature suggests this is not polio). There is no history of previous poliomyelitis to suggest a post-polio syndrome. The most common anterior horn cell disease would be ALS. The patient has no apparent cramps, fasciculations, or upper motor neuron findings that would further assist in localizing the lesion to the anterior horn cells and diagnosis of ALS. It is important to note that some forms of MN disease remain purely lower MN by symptoms and signs. Thus, MN diseases such as ALS remains a possibility.
There are various types of myopathy that present in this age range and with this pattern of weakness. The most common myopathy presenting after age 50 is IBM. About two-thirds of patients exhibit a characteristic pattern of weakness with early weakness and atrophy of the volar forearm muscles (wrist and finger flexors) with relative sparing of the deltoids. In the legs, there is early weakness and atrophy of the quadriceps in addition to the hip girdle and anterior tibial muscles. Asymmetric involvement is commonly seen. At least 30% to 40% of patients have dysphagia. The myopathy is very slowly progressive, so it fits well with the description. It is important to note that NCSs can sometimes demonstrate low amplitude sensory nerve action potentials (SNAPs) suggestive of an underlying axonal neuropathy even though patients are typically asymptomatic. EMG usually shows fibrillation potentials, positive sharp waves, and occasionally complex repetitive discharges and myotonic/pseudomyotonic discharges. A mixture of short duration, low amplitude polyphasic motor unit action potentials (MUAPs) and long duration, high amplitude, polyphasic MUAPs is often appreciated. The larger MUAPs may lead to the erroneous impression of chronic denervation with reinnervation, but in reality are secondary to the chronic myopathy. A way to help distinguish if large MUAPs are secondary to a myopathic versus neurogenic process is examine the recruitment pattern. In neurogenic disorders, MUAP recruitment is decreased (fewer units are seen and they fire fast) while with a myopathy, the pattern of recruitment is usually early (many units firing at a normal rate are seen with minimal power).

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Fibrillation</th>
<th>Other</th>
<th>Recruitment</th>
<th>MUAP Duration</th>
<th>MUAP Amplitude</th>
<th>Config</th>
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<tbody>
<tr>
<td>L=Left</td>
<td>R=Right</td>
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<td>L FDI</td>
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<td>R FDI</td>
<td>0-+</td>
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<td>Poor activation</td>
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<td>↓ and ↑</td>
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<td>L Triceps</td>
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<td>Poor activation</td>
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<td>++ Polyphasic</td>
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<td>↓</td>
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<tr>
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<td>NL</td>
<td>++ Polyphasic</td>
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<tr>
<td>L CPS</td>
<td>++</td>
<td>CRD</td>
<td>--</td>
<td>↓</td>
<td>↓</td>
<td>+ Serrated</td>
</tr>
</tbody>
</table>

APB = abductor pollicis brevis; BR = brachioradialis; CPS = cervical paraspinal; CRD = complex repetitive discharge; EIP = extensor indicis proprius; FCU = flexor carpi ulnaris; FPL = flexor pollicis longus; Infra = infraspinatus; MTP = myotonic potentials; MUAP = motor unit action potentials; NL = Normal; PT = pronator teres; RF = rectus femoris
Other myopathies are also possible and must be distinguished from IBM with a muscle biopsy.

**EVALUATION**

Serum creatine kinase (CK) can be helpful if markedly elevated but mild elevations may be seen in anterior horn cell disease (e.g., ALS) and normal CK can be seen in myopathies. So the serum CK of 1100 U/L is not particularly helpful.

In attempting to differentiate an anterior horn cell disorder from a myopathy, the most useful tests would be EMG/NCSs. The NCS revealed absent superficial peroneal and borderline to low amplitudes for the ulnar SNAPs bilaterally. The left ulnar-first dorsal intersosseous compound muscle action potential (CMAP) had an amplitude almost half the size of the right side. There was perhaps mild slowing of the left ulnar motor conduction velocity across the elbow, but not enough to declare it definitely abnormal. The left peroneal-tibialis anterior CMAP amplitude was also reduced, but interestingly, the peroneal-extensor digitorum brevis CMAP was normal. This finding would be atypical for a peripheral neuropathy, but might suggest reduction secondary to a distal myopathy.

The EMG revealed marked numbers of fibrillation potentials, positive sharp waves, complex repetitive discharges, and myotonic discharges. Notably, fasciculation potentials were not observed, which would be atypical for ALS. Myotonic discharges should lead to the consideration of myotonic dystrophy (DM1 and DM2), myofibrillar myopathies, and glycogen storage diseases (acid maltase, debrancher, branching enzyme deficiencies), but they can be seen occasionally in the inflammatory myopathies, including IBM. EMG of proximal muscles showed mainly small MUAPs. Some of the distal muscles had large MUAPs and decreased recruitment, suggestive of a possible superimposed neurogenic process (but could be seen in very severe myopathic weakness). The recruitment pattern was difficult to assess in many muscles due to poor activation or effort. The only strong evidence of a neurogenic process by EMG was in the ulnar-innervated muscle in the left arm. The EMG/NCS results were most consistent with a chronic necrotizing/irritative myopathic process, perhaps with superimposed left ulnar neuropathy and generalized axonal sensory polyneuropathy which are likely incidental to the myopathy, which is the primary problem.

A neuromyopathy related to sarcoidosis or granulomatous disease would need to be considered. Amyloidosis that can cause a myopathy and/or neuropathy could also be considered, although the patient did not have symptoms suggestive of amyloid polyneuropathy. Again, the clinical examination, laboratory testing, and EDX features are all consistent with a diagnosis of IBM, which is the most common myopathy in patients over age 50. It is likely that IBM would be on the top of the differential diagnosis.

To support this impression, a muscle biopsy of a clinically affected muscle would need to be performed. It is important to biopsy a muscle that is weak but not too weak, as severely weak muscles secondary to a neurogenic disorder can resemble a dystrophy on biopsy. It is also recommended to biopsy a muscle that was not studied by EMG. A vastus lateralis would probably be ideal in this case. On the biopsy, the focus would be on finding endomysial inflammation and invasion of non-necrotic muscle fibers, rimmed vacuoles, ragged red fibers/cytochrome oxidase negative fibers, amyloid deposition on Congo red or 15-21 nm tubulofilaments that would support the impression of IBM. Granulomas suggesting sarcoidosis or granulomatous neuromyopathy should be sought. The biopsy should also be helpful in distinguishing IBM from other myopathic disorders in the differential diagnosis (e.g., myofibrillar myopathy, dystrophy, and glycogen storage disorders).

**FOLLOW-UP**

Biopsy of the vastus lateralis muscle showed marked interstitial fibrosis and fat infiltration in atrophic muscle, focally and markedly infiltrated by lymphocytes. Other findings included numerous rimmed vacuoles and prominent intranuclear and cytoplasmic inclusions surrounded by vacuolar space. Granulomas were not seen. Acid and alkaline phosphatase reactions were intense in degenerating and regenerating fibers. The pathological diagnosis confirmed the clinical diagnosis of IBM.

The patient enrolled in an experimental trial of cyclosporine, but he noticed no difference in strength. At age 57 years, he underwent a left ulnar transposition at the elbow for focal neuropathy without subsequent benefit. There was continued generalized decline in strength and activities of daily living (ADLs), with accentuated weakness in the left hand and left foot dorsiflexors. He developed progressive dysphagia with occasional symptoms of aspiration. He enrolled in a National Institute of Health sponsored trial of a combination of prednisone, methotrexate, and azathioprine for the treatment of IBM, and continued on that regimen for about 6 years, the last 3 of which were after completion of the study. During these years, there was steady progression of weakness, and all drugs were gradually tapered and withdrawn.

At age 66, an otolaryngologist identified pooling of oral secretions in the piriform sinus and evidence of aspiration. This patient obtained modest benefit from an oral regimen of guaifenesin, but had recurrent frightening episodes of choking from thick secretions he could not mobilize from his oropharynx, due in part to a weak cough. At age 67, he underwent cricopharyngeal myotomy with marked symptomatic improvement of dysphagia and deglutition. By age 73, dysphagia had returned and spirometry identified hypoventilation on a restrictive basis. He started bilevel-positive pressure ventilation at that time to allow rest in the supine position at night. The patient died at age 74.

**Treatment for IBM**

To date, there are no clearly effective treatments that reverse, stabilize, or slow the progression of IBM. Many retrospective and few prospective studies have assessed the value of various immunosuppressant treatments. Several studies have documented improvement in elevated CK levels, but this was not associated
with sustained clinical improvement. An unblinded prospective study was performed on 11 patients, comparing prednisone plus either oral or IV methotrexate. Over 6 months, there was no significant change in clinical status, but serum CK levels dropped significantly.14

Intravenous immunoglobulin (IVIg) is clearly effective in the treatment of dermatomyositis.7 However, two prospective, double-blind, placebo-controlled studies have failed to demonstrate effectiveness in IBM.8,9 Methotrexate, which is effective in dermatomyositis and polymyositis, has also been shown to be ineffective in IBM as part of controlled trials.6

Two randomized controlled studies of β-Interferon-1a, each in 30 patients over a 6 month period, produced no significant improvement in strength or muscle mass.15,16 A trial of total body irradiation in IBM was ineffective and may have caused acceleration of the disease.13

Progressive dysphagia is a frequent complication of IBM. Medical treatment includes maneuvers such as chin tucking to maximize esophageal mechanics and the avoidance of offending foods, such as dry and particulate foods. Swallowing studies in some patients with progressive dysphagia demonstrate cricopharyngeal dysfunction, otherwise known as cricopharyngeal achalasia. The cricopharyngeus muscle (upper esophageal sphincter) is normally in a state of contraction, except when it relaxes in sequence with pharyngeal propulsion during the swallowing maneuver, to allow passage of the bolus into the esophagus. Primary cricopharyngeal dysfunction occurs when the muscle remains contracted during swallowing. This can occur on an idiopathic basis, but also develops in the setting of some neurological disorders, such as oculopharyngeal dystrophy, ALS, inflammatory myopathies, IBM, and stroke.

A number of pathological disorders in the oropharynx and esophagus develop in patients with polymyositis, dermatomyositis, and IBM, predisposing them to dysphagia and aspiration. These include dysfunctional pharyngeal wall motion (leading to poor bolus formation and transit in the oral phase), poor laryngeal elevation due to suprahypoid muscle weakness (impairing complete closure of the vestibule of the epiglottis and complete opening of the upper esophageal sphincter), inadequate hypopharyngeal pressure generation to trigger relaxation of the cricopharyngeus, and cricopharyngeal hypertrophy (resulting from fibrosis of the muscle), that leads to narrowing at the esophageal inlet.10 Fluoroscopic swallowing studies may demonstrate a “bar” during the swallowing maneuver that represents the hypertrophied cricopharyngeus and narrowing of the entry to the esophagus. For this reason, some patients benefit from cricopharyngeal myotomy, during which the muscle is sectioned to relieve the obstruction.10,19

Most of the treatment strategies for IBM aim to maximize mobility and dexterity, and minimize falls. Utensils with wide grips allow patients to feed themselves. Ankle-foot orthoses (AFOs) improve gait stability, but do not prevent falls from knee buckling. For that reason, most patients eventually lose the ability to ambulate.

Rehabilitation Treatment Issues in IBM

Since there is no cure for IBM, most of the current treatment strategies are designed to maximize mobility and dexterity functions, minimize falls and other potential complications related to the disease, and aim for improved quality of life for the patients.

A multi-disciplinary team approach to treating patients with IBM (as it is often the case with other neuromuscular diseases) is recommended whenever possible. Even though IBM is a primary muscle disease, the functional and quality of life impact it has on patients with IBM can be quite significant. Although not all disciplines need to be involved at once or initially in the disease course, as the disease progresses, a coordinated care plan needs to incorporate various clinical specialists including: a physical therapist, an occupational therapist, an orthotist, a speech therapist, a rehabilitation psychologist, a social worker, a pulmonologist, a gastroenterologist, a nutritionist, and an otolaryngologist. Examples of the various clinical specialists and their roles in the multidisciplinary team are shown (Table 3). Often a physical medicine and rehabilitation specialist or a neurologist will lead the treatment team and coordinate a comprehensive, goal-oriented care plan.

Often, the affected muscle groups in IBM are primarily finger flexors and knee extensors. The progressive weakness affecting the finger flexors have great impact on ADLs and self-care (oral hygiene, grooming, dressing, feeding, and bathing), while knee extensor weakness results in impaired mobility with frequent falls due to knee buckling. Adaptive equipment such as built-up handle utensils, electric toothbrushes or razors, handheld shower, grabbers, and sockaids can help improve patient’s independence. An AFO with articulated ankle joint with dorsiflexion assist and anterior stop can help with weak tibialis anterior muscle as well as quadriceps muscle weakness. During the swing phase of the gait, the dorsi-assist action of the AFO will help with toe clearance while during the stance phase, the anterior dorsiflexion stop will help to keep the knee from buckling by prevention of ankle dorsiflexion. Another option may be a lightweight non-articulated (solid ankle) AFO with ankle joint at neutral position. A forearm style crutch with built-up handle (to compensate for finger flexor weakness) may also be used in select ambulatory patients with IBM to improve their gait and balance. Wheeled walkers or quad canes may also help, depending on the degree and pattern of weakness. As the disease progresses, mobility and ADL functions decline, the risk of falls increases. Timely and appropriate prescription for mobility and transfer equipment (with help from therapists) will improve safety and independence while decreasing complications.

Until recently, active physical exercise in patients with inflammatory myopathies was discouraged for fear of exacerbating muscle inflammation. Although exercise studies are limited in IBM and report only a few subjects,15,18 there appears to be an overall trend towards achieving health benefits and reducing physical impairment with improved strength measures, without significant aggravation of muscle inflammation. A moderate intensity 20 min home exercise program combined with a 15 minute walk 5 days a week for 12 weeks showed that while strength was not significantly improved after the exercise program, none of the patients
deteriorated in regard to muscle function. Serial muscle biopsies and CK levels were used for safety assessments. The pre- and post-exercise program muscle histopathology was unchanged and there were no signs of increased muscle inflammation. In addition, the CK levels were unchanged. Continued home stretching programs are recommended to maintain range of motion in the joints and should be incorporated into a daily exercise regimen.

Recently, an IBM disease specific 10 item functional rating scale (IBMFRS) was introduced by the Muscle Study Group based partly on the ALS Functional Rating Scale. It was shown to be relatively quick, simple, and does not require extensive training for the evaluator or expensive equipment. It appears to correlate well with traditional measures of efficacy and is sensitive to changes in IBM disease severity. The development of the IBMFRS should be of great help with clinical trials in IBM and the evaluation of efficacy of various potential treatments and therapies.

Table 3 Examples of clinical specialists and roles in multidisciplinary team

<table>
<thead>
<tr>
<th>Evaluation/Education</th>
<th>Treatment/Equipment</th>
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</thead>
<tbody>
<tr>
<td>Physical Therapist (PT)</td>
<td>Mobility assessment</td>
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<tr>
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<td>Exercise and ROM education</td>
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<td>Transfer eval and education</td>
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<td>Occupational Therapist (OT)</td>
<td>ADL assessment</td>
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<td>Adaptive equipment evaluation</td>
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<td>Home evaluation</td>
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<tr>
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<td>Evaluation, manufacture, and fitting of orthosis</td>
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<td>Safe swallowing techniques</td>
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<td>Swallowing evaluation</td>
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<td>Work related issues</td>
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<td>Discussion re: prolonged ventilation options</td>
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<td>Diet counseling</td>
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<td>Otolaryngologist</td>
<td>Tracheostomy evaluation</td>
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<tr>
<td></td>
<td>Dysphagia evaluation</td>
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</tbody>
</table>

ADL = activities of daily living; AFOs = ankle foot orthosis; BIPAP = bilevel positive airway pressure; PEG = percutaneous endoscopic gastrostomy; RLD = restrictive lung disease; ROM = range of motion

REFERENCES
