Neuromuscular Update I

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Dr. Levin received his bachelor’s degree and his medical degree from Johns Hopkins University in Baltimore, Maryland. He then performed a residency in internal medicine at University Hospitals of Cleveland, followed by a neurology residency at the University of Chicago Hospitals, where he served as chief resident. He is currently chairman of the Department of Neurology and director of the Neuromuscular Center at Cleveland Clinic. Dr. Levin is also professor of medicine at the Cleveland Clinic College of Medicine of Case Western Reserve University. His current research interests include electromyography, radiculopathy, myasthenia gravis, and polyneuropathy.

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Dr. Salajegheh received his medical degree from Tehran University of Medical Sciences in 1995 and completed his training in neurology at the University of Massachusetts Medical School in 2003. He finished four years of fellowship training in neuromuscular disease, two years at the National Institutes of Health and another two years at Brigham and Women’s hospital, and is board certified by the American Board of Medical Specialties in both Neurology and Neuromuscular Medicine. He is currently a member of the faculty at Harvard Medical School and a staff member in the Department of Neurology at Brigham and Women’s Hospital. He is actively involved in clinical research on muscle channelopathies as well as both clinical and laboratory based research focused on studying the mechanisms of inflammatory myopathies.

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Neuromuscular Update I

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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. After attending both sessions, 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 focal mononeuropathy, systemic disease and neuromuscular disorders, and exercise-induced cramps.

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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CASE DESCRIPTION

History

A 48-year-old man underwent a left total knee arthroplasty and awoke from surgery with a complete left foot drop and loss of sensation over the lateral calf and dorsum of the foot. He was given physical therapy, including electrical stimulation, without benefit. An ankle foot orthosis (AFO) was issued and has been used since that time. He has tried electrical stimulation since then, but it was without benefit. There has been no improvement in his foot drop since the onset of symptoms.

The patient's medical history was pertinent for left foot weakness following lumbar laminectomy 6 years before. The patient reported complete resolution of foot weakness shortly thereafter.

He sought neuromuscular consultation 5 months after onset of left foot drop. At that time, he reported continued paresthesia in the same distribution, without pain.

Examination

Power was normal except for the left leg in the following muscles:

- Foot Dorsiflexion: 2/5
- Foot Eversion: 4/5
- Toe Extension: 2/5
- Toe Flexion: 4+/5
- Plantar Flexion: 5-/5

Sensation to pinprick was severely impaired over the left lateral calf and dorsum foot to pin sensation. There was a prominent left foot drop gait. Muscle stretch reflexes were 2+ throughout except for the left ankle jerk, which was 1+.

Evaluation

The patient's electromyography (EMG) examination, performed 5 months after the onset of symptoms, is detailed in Table 1. The interpretation of this study was not straightforward. When nerve conduction studies and needle EMG are taken together, the picture is most consistent with severe, chronic, and active motor axon loss in the left L5 root distribution below the knee, with additional involvement of the left H reflex and medial gastrocnemius muscle, suggesting the presence of S1 involvement. Unclear features of this study include the following:

1. Root level lesions of this severity should have demonstrated motor axon loss in posterior thigh muscles innervated by the L5 and S1 roots.
2. A peroneal nerve lesion at the knee/fibular head could coexist, but the bilateral absence of the superficial peroneal sensory responses does not allow for a clear diagnosis.
3. The absence of posterior thigh involvement on needle EMG raises the question of sciatic nerve lesion below the mid thigh, but the sural sensory response would be expected to be abnormal in that setting.
### Needle EMG Summary

<table>
<thead>
<tr>
<th>Side</th>
<th>Muscle</th>
<th>InsAct</th>
<th>Fib</th>
<th>PW</th>
<th>Fasc</th>
<th>Other</th>
<th>Number</th>
<th>Recruit</th>
<th>Dur</th>
<th>Dur.</th>
<th>Amp</th>
<th>Amp.</th>
<th>Poly</th>
<th>Poly.</th>
<th>Descript</th>
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<tbody>
<tr>
<td>Left</td>
<td>Rectus Fem.</td>
<td>norm</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1-</td>
<td>Mod</td>
<td>Few</td>
<td>1+</td>
<td>Few</td>
<td>1+</td>
<td>1+</td>
<td>NC</td>
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<tr>
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<td>2+</td>
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<td>-</td>
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<td></td>
<td></td>
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<tr>
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<td>Semitend.</td>
<td>norm</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1-</td>
<td>Mod - V</td>
<td>Norm</td>
<td>Norm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>EDB</td>
<td>2+</td>
<td>2+</td>
<td>0</td>
<td>MTP</td>
<td>-</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>Gluteus Med.</td>
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<td>0</td>
<td>0</td>
<td>1-</td>
<td>Mod</td>
<td>Few</td>
<td>1+</td>
<td>Norm</td>
<td>NC</td>
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<td>2+</td>
<td>0</td>
<td>3-</td>
<td>Rapid</td>
<td>Most</td>
<td>1+</td>
<td>Few</td>
<td>1+</td>
<td>1+</td>
<td>1+</td>
<td>NC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>Tib Post</td>
<td>2+</td>
<td>1+</td>
<td>0</td>
<td>SMU</td>
<td>Rapid</td>
<td>All</td>
<td>1+</td>
<td>All</td>
<td>1+</td>
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<td>Mod</td>
<td>Norm</td>
<td>Norm</td>
<td>NC</td>
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<tr>
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<td>Biceps S.H.</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td>0</td>
<td>0</td>
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<td>Rapid</td>
<td>Most</td>
<td>2+</td>
<td>Most</td>
<td>1+</td>
<td></td>
<td>NC</td>
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</tr>
<tr>
<td>Left</td>
<td>AH</td>
<td>0+</td>
<td>1+</td>
<td>0+</td>
<td>3-</td>
<td>Mod - R</td>
<td>Some</td>
<td>1+</td>
<td>Some</td>
<td>1+</td>
<td>Some</td>
<td>1+</td>
<td>NC</td>
<td></td>
<td></td>
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<tr>
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<td>Tibialis Ant.</td>
<td>norm</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1-</td>
<td>Mod - R</td>
<td>Some</td>
<td>1+</td>
<td>Some</td>
<td>1+</td>
<td>1+</td>
<td>NC</td>
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<td>0</td>
<td>0</td>
<td>3-</td>
<td>Mod</td>
<td>Most</td>
<td>1+</td>
<td>Most</td>
<td>1+</td>
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<td>NC</td>
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</table>

### HReflex Summary Table

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Stimulus</th>
<th>Recording</th>
<th>Side</th>
<th>Wave</th>
<th>Lat</th>
<th>Amp</th>
<th>H-Reflexes</th>
<th>Lat</th>
<th>Amp</th>
<th>(ms)</th>
<th>(mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibial</td>
<td>Pop. Fos.</td>
<td>Soleus</td>
<td>Left</td>
<td>All</td>
<td>4.67</td>
<td>6.92</td>
<td>34.67</td>
<td>1.22</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Tibial</td>
<td>Pop. Fos.</td>
<td>Soleus</td>
<td>Right</td>
<td>All</td>
<td>5.83</td>
<td>12.70</td>
<td>33.00</td>
<td>5.05</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Sensory Side-To-Side Comparison Table

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Stimulus</th>
<th>Recording</th>
<th>B-PAmp</th>
<th>LatNPk</th>
<th>CV</th>
<th>Dist</th>
<th>Norm B-PAmp</th>
<th>Norm LatNPk</th>
<th>Temp (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sural</td>
<td>Mid Calf</td>
<td>Ankle</td>
<td>4.39</td>
<td>3.77</td>
<td>3.60</td>
<td>50.0</td>
<td>48.3</td>
<td>140</td>
<td>30.2</td>
</tr>
<tr>
<td>Peroneal</td>
<td>Lower</td>
<td>Ankle</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

### Motor Side-To-Side Comparison Table

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Stimulus</th>
<th>Recording</th>
<th>B-PAmp</th>
<th>LatOn</th>
<th>CV</th>
<th>Dist</th>
<th>Norm B-PAmp</th>
<th>Norm LatOn</th>
<th>Temp (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroneal</td>
<td>Ankle</td>
<td>EDB</td>
<td>NR</td>
<td>2.26</td>
<td>5.08</td>
<td>NR</td>
<td>70</td>
<td>3.22</td>
<td>29.7</td>
</tr>
<tr>
<td>Tibial</td>
<td>Ankle</td>
<td>AH</td>
<td>3.12</td>
<td>2.50</td>
<td>5.83</td>
<td>4.25</td>
<td>80</td>
<td>6.79</td>
<td>29.7</td>
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</tbody>
</table>

### HReflex Summary Table

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Side</th>
<th>Recording</th>
<th>Wave</th>
<th>Lat</th>
<th>Amp</th>
<th>H-Reflexes</th>
<th>Lat</th>
<th>Amp</th>
<th>(ms)</th>
<th>(mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibial</td>
<td>Left</td>
<td>Soleus</td>
<td>All</td>
<td>5.83</td>
<td>12.70</td>
<td>33.00</td>
<td>1.22</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AH = abductor hallucis; Amp = amplitude; ATR = atrophy; Biceps S. H. = biceps short head; (C) = celsius; CV = conduction velocity; Dist = distal; Dur = duration; EDB = extensor digitorum brevis; Fasc = fasciculations; Fib = fibrillations; Fib. Head = fibular head; Gastroc. Med. H. = gastrocnemius medial head; Gluteus Med. = gluteus medius; L = left; Lat. = lateral; MTP = metatarsophalangeal; n/a = not available; NR = no response; Paroneus Ln = paroneus longus; Poly = polyphasic; Pop. Fos. = Popliteal Fossa; PW = positive waves; R = right; Recruit = recruitment; Rectus Fem. = rectus femoris; SMU = single motor unit; Tibialis ant. = tibialis anterior; Tibialis post. = tibialis posterior.
DIFFERENTIAL DIAGNOSIS

Although most causes of foot drop are due to peripheral nerve lesions, the differential diagnosis is wide (Table 2). The typical electrodiagnostic (EDX) patterns of peroneal neuropathy have been described.\(^1\)

<table>
<thead>
<tr>
<th>Table 2: Differential Diagnosis of Foot Drop</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peripheral Nerve Disorders</strong></td>
</tr>
<tr>
<td>• Deep peroneal neuropathy</td>
</tr>
<tr>
<td>• Common peroneal neuropathy</td>
</tr>
<tr>
<td>• Sciatic neuropathy</td>
</tr>
<tr>
<td>• Lumbosacral trunk neuropathy</td>
</tr>
<tr>
<td>• Lumbosacral plexopathy</td>
</tr>
<tr>
<td>• Anterior horn cell disease</td>
</tr>
</tbody>
</table>

**Muscle Disorders**\(^5\)

• Scapuloperoneal dystrophy
• X-linked Emery-Dreifuss muscular dystrophy
• Facioscapulohumeral dystrophy
• Hereditary inclusion body myositis
• Welander distal myopathy
• Udd distal myopathy
• Markesbery-Griggs distal myopathy
• Myofibrillar myopathy

**Neuromuscular junction disorders**
• Myasthenia gravis

**Myelopathy**

• Multiple sclerosis
• Compressive myelopathy

**Cerebral Disorders**

• Sagittal inter-hemispheric lesions (meningioma, other tumors)

Foot Drop in Sciatic Neuropathy

Depending on the severity and nature of the sciatic nerve injury, foot drop and peroneal distribution weakness may be the primary manifestations of this disorder. In spite of relatively similar pathways in the thigh and popliteal fossa, the peroneal and tibial nerves have strikingly different vulnerabilities to injury. When exposed to the same forces, the peroneal nerve suffers more damage than the tibial nerve in almost all cases. A number of anatomical and vascular differences partially explain this tendency.

First, below the bifurcation of the sciatic nerve in the thigh, the peroneal nerve travels in a single large bundle of nerve fibers, and its arterial supply rests exposed on its surface.\(^2\) In contrast, the tibial nerve is composed of multiple small bundles, with its main arterial vascular supply occupying crevices between the bundles. This orientation decreases the effect of any compressive force on the tibial nerve fibers and vessels. Additionally, in the popliteal fossa, the tibial nerve receives more nutrient arteries than the peroneal nerve due to its closer proximity to the popliteal artery.\(^3\)

Second, except in the most proximal aspect of the popliteal fossa, the tibial nerve is more deeply situated and less exposed than the peroneal nerve to external sources of compression.

Third, structural differences increase risk to the peroneal division of the sciatic nerve. There is less connective tissue and adipose between fascicles of the peroneal nerve, providing less protection. The peroneal nerve appears to be more fixed in position than the tibial nerve, allowing it less give when stretched or distorted in instances such as surgery. The peroneal nerve is more fixed by its adjoining tissues at the sciatic notch and the fibular head, while the tibial nerve appears to be fixed in large part only by the muscles it innervates.\(^3\)

For these reasons, some sciatic nerve lesions will masquerade as peroneal lesions. The classical example of this is the sciatic neuropathy due to stretch injury during total hip arthroplasty. While the main clinical and EDX features will be those of peroneal neuropathy, comprehensive studies will demonstrate asymmetry of the sural and H-reflex amplitudes when compared with the uninvolved side.

L5 Radiculopathy With Involvement of the Superficial Peroneal Sensory Response

A major EDX difference between L5 radiculopathy and peroneal neuropathy is the involvement of nonperoneal muscles including tibialis posterior, flexor digitorum longus, semitendinosus, tensor fascia lata, and gluteus medius. When first working up the patient with foot drop in the EMG laboratory, finding low-amplitude peroneal compound muscle action potential responses triggers superficial peroneal sensory studies. In a small group of patients, the superficial peroneal sensory response is asymmetrically low, causing confusion when the needle EMG shows a pattern of axon loss in the L5 root distribution.

Two lesions can demonstrate this pattern.\(^4\) Injury to the lumbosacral trunk (Furcal’s nerve), a structure composed of the extraspinal anterior primary ramus of the L5 (and sometimes the L4) sensory and motor nerve fibers, will result in axon loss along both the motor and sensory L5 fibers. This can be seen in some focal compressive nerve lesions in the pelvis, and is also a manifestation of focal diabetic neuropathy.

In up to 30% of individuals, the L5 dorsal root ganglion is in an intraspinal location and not within the intervertebral foramen, where it is usually protected from compressive injury. As a result, in those individuals, the L5 dorsal root ganglion is vulnerable to compressive injury within the intraspinal canal, with resultant loss of the superficial peroneal sensory response when axon loss occurs.

EVALUATION

Given the proximity of the patient’s symptom onset to his knee replacement surgery, the lack of back pain suggestive of a lumbosacral...
radiculopathy, and EDX findings, a distal sciatic mononeuropathy preferentially affecting the peroneal division was thought to be the most likely etiology for his foot drop, versus combined common peroneal and tibial mononeuropathies.

In order to aid in more precise localization, neuromuscular ultrasound (NMUS) was utilized to assess the sciatic, peroneal, and tibial nerves for evidence of transection, entrapment, or adjacent pathology affecting the nerves (e.g., hematoma, scar tissue, bone fragments, etc.). The study revealed the nerve to be intact and without significant increase in cross-sectional areas, suggestive of entrapment. However, a hypoechoic area surrounding the peroneal nerve at the fibular head and significant subcutaneous tissue swelling within the popliteal fossa adjacent to the peroneal/tibial divisions of the sciatic nerve were noted.

NMUS is an adjunct to electrophysiological studies that yields valuable and often diagnostic structural information. A recent study examined outcomes when NMUS is added to EDX testing in the mononeuropathy evaluation. Diagnosis and treatment were meaningfully impacted in 26% of cases, including identification of nerve tumors, adjacent pathology (e.g., synovial cysts), and variant anatomy responsible for the patient’s symptoms. In 47%, findings supported the EDX test impression, but did not impact treatment (e.g., focal nerve swelling at an entrapment site identified by EMG). Other cases were considered “inconclusive” (i.e., no definite abnormalities identified), although the lack of evidence of nerve entrapment and exclusion of relevant adjacent pathology obviously did yield useful clinical information in these cases. Overall, the study supported the notion that NMUS can meaningfully impact patient care when combined with the EMG in selected patients.6 With regards to surgical planning, NMUS has been demonstrated to characterize complete nerve transection with a sensitivity of 89%, and a 95% specificity.7 Identifying stump neuromas, localizing of the proximal/distal nerve stumps, and revealing excessive perineural scar tissue in chronic cases can also be accomplished.8,9

MANAGEMENT

After extensive discussion with the patient and his family regarding management options, it was decided to take the patient to the operating room for exploration of the left distal sciatic nerve and common peroneal nerve. Intraoperatively, the common peroneal nerve was found to be surrounded by hematoma and scar tissue at the fibular neck. The distal sciatic nerve was grossly unremarkable in appearance. External neurolysis was performed, and nerve action potentials (NAPs) were recorded. NAPs were present at all sites proximal, across, and distal to the fibular head.

The presence of NAPs beyond an injury site indicates preserved axonal function or significant axonal regeneration. NAP recordings can show regenerative changes across a lesion in continuity as early as 6 to 8 weeks after focal injury; thus providing useful information earlier than clinical examination or standard EDX studies.10 Due to intact NAPs identified in the described patient, grafting was not performed.

REHABILITATION ISSUES

The patient was last assessed at 7 months after symptom onset and had no improvement in his foot drop at that time. He continues to wear a left AFO and participates in physical therapy, including water therapy.

While the presence of NAPs distal to the injury site indicates the potential for further recovery, the patient clearly has a long-term neurologic deficit. He will need bracing that is custom suited to his needs. An off-the-shelf AFO is not appropriate. Orthotic management is directed toward correcting the foot drop to improve safety of ambulation and increase endurance.11 If further recovery is achieved, other options might include a high-top shoe or boot, which may be good choices for patients with some preservation of function or for those recovering from more severe deficits.

Nonarticulated plastic AFOs fabricated in a neutral position offer lightweight, durable, and relatively good cosmesis. While often sufficient to improve gait, the nonarticulated AFO may prevent normal planter flexion at initial heel contact and limit tibial progression (i.e., dorsiflexion) during stance.12 The absence of plantar flexion at heel strike decreases shock absorption and may cause knee instability by creating a flexor moment at the knee in early stance. This is especially problematic in a patient with weak knee extensor musculature, which is not the case here.

A cushioned heel on the shoe improves shock absorption and aids in stabilizing the knee by decreasing the knee flexor moment. In addition, lack of tibial progression may cause a knee extensor moment in late stance, interfering with knee flexion in early swing. These problems may be minimized by use of a posterior leaf spring or flexible plastic AFO. This AFO has posterior trim lines, allowing the plastic to flex during stance and recoil in swing.12 However, it provides minimal mediolateral stability, less durability, and will not protect against an inversion sprain. This patient does have reasonable strength in eversion and inversion, so may consider this as an option. A plastic articulated AFO with a dorsiflexion assist improves shock absorption, smoothness of gait, and tibial progression.

Mild plantar flexion weakness may be seen in combination with dorsiflexion weakness and mediolateral instability. Plantar flexion weakness is detected during single-foot heel rises. The patient usually requires the assistance of the examiner to balance while standing on one foot. Ten complete heel rises reflect normal strength. Patients with subtle weakness may attempt to compensate by “hopping” (initiating the upward movement by extending a flexed knee and hip) or by utilizing elbow extension (pushing down on the examiner’s hands). With more severe weakness, the patient has difficulty walking on their toes, or may report difficulty walking up hills or stairs. The addition of mild plantar flexion weakness often results in an inability to control tibial progression (e.g., ankle dorsiflexion) during mid and terminal stance. Careful gait analysis may reveal increased dorsiflexion in terminal stance as well as a delayed heel rise.12 Normally, heel rise occurs just before contralateral heel strike and the knee is near full extension in terminal stance. In turn, increased dorsiflexion causes a minimal amount of knee flexion in terminal stance. Mild plantar flexion
weakness slows the progression of the body, resulting in a decreased velocity and step length.

In addition to managing dorsiflexion weakness and mediolateral instability, limiting dorsiflexion in terminal stance assists with plantar flexion weakness that should normalize heel rise and improve velocity and step length. A stiff, nonarticulated plastic AFO accomplishes these goals. Anterior trim lines, thicker gauge plastic or carbon fiber reinforcements supply the additional stiffness. However, patients may complain of the disadvantages of nonarticulating plastic AFOs with skin irritation or pain from the anterior tibial strap as it resists dorsiflexion. Extra width and padding on the strap can improve comfort, and the use of an assistive device such as a cane, crutches, or walker may also be helpful.

A more comfortable option is an articulating plastic AFO with a dorsiflexion assist spring, anterior trim lines, and a stop set at approximately 5 degrees of dorsiflexion. The stop simulates gastrocnemius soleus function by preventing excessive dorsiflexion at terminal stance. This normalizes heel rise resulting in an increased step length and gait velocity. Foot clearance during swing is not compromised at 5 degrees of dorsiflexion.

REFERENCES
CASE 1 DESCRIPTION

History

A 58-year-old man presented with difficulties going up stairs for 2 years. More recently, he had also noted proximal arm weakness. The symptoms were symmetrical, and he reported no sensory loss or paresthesias. The patient described intermittent mild dysphagia, thought to be related to esophageal strictures, but reported no other bulbar symptoms. He had mild myalgias limited to the lower back. His previous medical history was notable for simvastatin treatment for hypercholesterolemia. The simvastatin use antedated weakness by several years, and despite stopping medication a few months after weakness began, his problems continued to worsen. He was also taking warfarin prophylactically for elevated anticardiolipin antibody titers, but had no documented episodes of prior thrombosis. No other family members had ever experienced similar problems.

Examination

The patient had normal skin and an otherwise unremarkable general physical examination. Neurologically, he was alert with normal cognition. Cranial nerves were intact. He had no muscle atrophy. Shoulder abduction was mildly weak, Medical Research Council (MRC) grade 4+. Strength was otherwise normal in the upper extremities. In the legs, there was mild (MRC 4+) weakness of bilateral hip and knee flexion, and bilateral foot dorsiflexion. Sensation and deep tendon reflexes (DTRs) were normal. He had mild difficulty arising from a kneeling position on the floor. His gait was normal.

Prior Studies

Serum creatine phosphokinase (CPK) was 2300 IU/L (normal < 204 IU/L). Erythrocyte sedimentation rate, anti-nuclear antibody, anti SSA/SSB antibodies, thyroid stimulating hormone, comprehensive metabolic panel, and complete blood count (CBC) were normal. Rheumatoid factor was mildly elevated at 36.2 IU/mL (normal < 13.9 IU/mL). Nerve conduction studies (NCSs) showed mildly reduced sural sensory nerve action potential (SNAP) and peroneal compound muscle action potential (CMAP) amplitudes. Conduction velocities were normal in these nerves. Tibial CMAP amplitudes were in the low normal range with mildly slowed conduction velocity. Needle electromyography (EMG) examination of weak leg muscles demonstrated fibrillation and positive sharp wave potentials at rest and small amplitude, short duration, polyphasic voluntary motor unit action potentials (MUAPs). There was evidence of early recruitment in weak muscles.

Current studies

Chest X-ray revealed mediastinal adenopathy. After discontinuation of warfarin a quadriiceps muscle biopsy was performed. The results of other histologic studies will also be revealed later in the manuscript.
CASE 2 DESCRIPTION

History

A 78-year-old woman presented with 4 days of nausea, vomiting, fever, chills, right upper quadrant pain, and 10 to 14 days of progressive arm and hand weakness. Weakness began in the left hand but spread to the right side within days. Lower-leg weakness followed within several days of arm and hand involvement. The acute symptoms had been preceded by intermittent joint and wrist pain for several months, but she had not sought medical advice for this complaint. Her previous history was notable for atrial fibrillation treated with warfarin. In 1955, she underwent lobectomy for tuberculosis which was complicated by an episode of transfusion related jaundice. There was also a history of intermittent petechiae in the legs for 10 years.

Examination

She appeared ill and had mild hepatomegaly. On neurological examination, she followed commands appropriately. Cranial nerves were normal. The proximal arms were mildly weak (MRC 4+). In the hands, she had prominent wrist drop and finger abduction weakness (MRC 1) bilaterally and milder weakness of thumb abduction (MRC 4). The proximal legs were mildly weak (MRC 4+). Foot dorsiflexion was severely weak (MRC 3), and plantar flexion was moderately weak (MRC 4). Reflexes were 2+ in the arms. Patellar reflexes were 1+ and Achilles reflexes were absent. Plantar responses were flexor. She had decreased pinprick and vibratory sensation in the lower legs and fingers.

Prior Studies

Previous testing had demonstrated normal electrolytes and CBC. Her alanine aminotransferase was elevated at 158 U/L. Aspartate aminotransferase, alkaline phosphatase, and total bilirubin were normal. Urinalysis was normal. Additional testing showed an elevated antinuclear antibody titer of 1:640 and elevated rheumatoid factor of 1:2560. The C3, C4, and CH50 were reduced. No serum antineutrophil cytoplasmic antibodies were detected. Serum Lyme antibodies were identified, and she received 21 days of ceftriaxone treatment for this. Human immunodeficiency virus (HIV) testing was negative. The cerebrospinal fluid had mildly elevated protein (59 mg/dL), but was acellular.

Current Studies

NCSs showed an absent left sural SNAP and absent left median, ulnar, radial, and right radial SNAPs. No left ulnar CMAP was recordable. The left median CMAP amplitudes were mildly reduced, and the left radial CMAP amplitudes were severely reduced with normal conduction velocities. The left peroneal CMAP was not recordable from the extensor digitorum brevis, but a small CMAP was recorded from the tibialis anterior muscle. The left tibial CMAP amplitude was in the low normal range with normal conduction velocity. Needle EMG examination of select left hand and lower leg muscles showed abnormal spontaneous activity (fibrillations and positive sharp waves) in the leg with markedly reduced recruitment. Similar changes were observed in weak muscles of the left hand. Further serologic and histologic studies will be described later.

CASE 1 DIFFERENTIAL DIAGNOSIS

These two cases highlight the importance of recognizing the relationship of neuromuscular (NM) symptoms to systemic illnesses. In the first case, the patient had chronic progressive weakness of proximal muscles accompanied by myalgia. With normal reflexes and in the absence of significant sensory loss, the clinical findings strongly suggested a myopathic condition. The laboratory evaluation showing elevated CPK and electrodiagnostic (EDX) testing confirmed myopathic changes and provided further evidence of muscle disease. Several possibilities are important to consider in this situation.

Acquired Muscle Disorders

Inflammatory muscle disease is the most likely category of disorders presenting with this clinical history in this age range. Possible causes include infections, polymyositis (PM), dermatomyositis(DM), inclusion body myositis (IBM), and overlap syndromes in which muscle inflammation is associated with other immune system disorders such as systemic lupus erythematosus (SLE), scleroderma, Sjögren syndrome, rheumatoid arthritis (RA), mixed connective tissue disease, or sarcoidosis. Most chronic inflammatory muscle disorders are more common in women, except for IBM, which more often occurs in older men.

Among the acquired inflammatory myopathies, DM is usually the most easily recognized clinically because of a characteristic skin rash that precedes or accompanies muscle weakness. Patients develop periorbital edema with a purplish color on the eyelids (heliotrope rash), erythematous, papular, scaly lesions on the knuckles (Gottron’s papules), and erythematous rash on the face, neck, chest and upper back, and extensor surfaces of large joints. Calcifications may occasionally occur in the subcutaneous tissue over pressure points. Weakness usually involves axial and proximal limb muscles in a relatively symmetrical distribution. Some patients may not have a rash or may have very subtle skin changes that can result in an erroneous diagnosis of PM. Like DM, the distribution of muscle weakness in PM involves axial and proximal limb muscles. The onset may be more insidious and patients have no rash, making the diagnosis of an inflammatory myopathy less obvious. The onset of IBM is similarly insidious and typically results in both proximal weakness, especially of the quadriceps muscles, and characteristic wrist and finger flexor weakness.
Weakness may be asymmetrical, in contrast to the usual pattern in DM and PM.

Inflammatory myopathy may be associated with other systemic diseases such as connective tissue disorders, sarcoidosis, or infections. Patients with scleroderma, Sjögren syndrome, SLE, RA, and mixed connective tissue disorders may have myositis that looks clinically like PM or more rarely DM. Sarcoïdosis is well known to involve muscle, with more than half of patients demonstrating granulomas on muscle biopsy. However, most patients have no complaints of muscle weakness. When initial symptoms of sarcoidosis relate to granulomatous myositis, patients may have no clinical features that differentiate them from individuals with PM.

Infectious agents may directly cause muscle damage and inflammation, or can trigger immune-mediated damage without directly infecting muscle. Numerous agents have been implicated including bacteria, mycobacteria, fungi, parasites, and viruses. Patients who have myositis related to infections typically present more acutely with recent or active symptoms of systemic infection.

**Genetically Mediated Muscle Disorders**

In an older patient with no family history of muscle weakness, metabolic myopathies or muscular dystrophies are less likely than acquired causes of myopathy. In younger adults in whom only chronic myopathic changes are identified on biopsy, consideration may be given to genetic conditions such as mitochondrial myopathies, or adult onset dystrophies, such as some limb girdle variants, fascioscapulohumeral muscular dystrophy (FSHD), or oculopharyngeal muscular dystrophy (OPMD). Many patients with these disorders who are diagnosed later in life can, in retrospect, describe subtle problems that may have been ignored or ascribed to other causes.

The pattern of weakness or coexistence of other medical problems may provide clues to the diagnosis. For example, patients with FSHD typically have facial weakness with associated hip and shoulder girdle weakness, and OPMD patients have prominent ptosis, ophthalmoplegia, and dysphagia with limb weakness. Although routine muscle biopsy may be nondiagnostic, immunohistochemistry can sometimes help define underlying protein defects, and genetic tests are commercially available for many adult onset dystrophies.

**Diagnostic Studies**

Transbrachial biopsy showed non-caseating granulomas characteristic of sarcoidosis. The angiotensin converting enzyme level was 41 U/L (normal < 67 U/L).

For the patient in case 1, the negative family history and his older age made a genetic disorder less likely. The was also no history of an infectious cause for myopathy. Systemic markers of inflammation were notable only for the mildly elevated rheumatoid factor which did not correlate with symptoms of joint pain or other vasculitic or connective tissue disease. In this case, the muscle biopsy was the diagnostic test, leading to identification of his underlying sarcoidosis.

Additional testing confirmed more widespread but asymptomatic involvement in the mediastinal lymph nodes.

**CASE 2 DIFFERENTIAL DIAGNOSIS**

The second patient’s syndrome of hand and arm weakness and sensory loss that subsequently spread to involve legs and feet was consistent with peripheral nerve disease. The condition was relatively fast moving with initially asymmetrical, nonlength-dependent involvement suggesting discrete, multifocal areas of nerve injury characteristic of mononeuropathy multiplex. Patients with known underlying primary vasculitis or connective tissue disorders, present less diagnostic difficulty than those who have peripheral neuropathy as the first symptom of systemic disease. In this case, there was no known history of a contributory systemic illness. Diagnostic considerations in this situation include primary systemic vasculitides, vasculitis associated with connective tissue disorders, hypersensitivity and infectious vasculitis, and paraneoplastic vasculitis.

**Primary Systemic Vasculitis**

Polyarteritis nodosa, Churg-Strauss syndrome, microscopic polyangiitis, and Wegener’s granulomatosis may all result in epineural or perineural arteriolar inflammation and ischemic damage to neurons. The disorders are distinguished by the caliber of blood vessels involved, as well as the associated clinical symptoms. In polyarteritis nodosa, medium and small muscular arteries are affected. Symptoms may include weight loss, skin changes, myalgias, and renal dysfunction. Up to 50% of patients may have coexisting hepatitis B infections, which may be associated with especially aggressive nerve disease. Peripheral nerve involvement most often manifests as an ischemic mononeuropathy which may progress to multiple mononeuropathies. Painful, patchy, and asymmetrical involvement is characteristic.

The neuropathy in Churg-Strauss, Wegener’s granulomatosis, and microscopic polyangiitis may be clinically indistinguishable from the pattern observed in polyarteritis nodosa, but other features of these syndromes help to distinguish them from polyarteritis nodosa. Unlike polyarteritis nodosa, smaller vessels may be involved, including venules and capillaries in addition to arterioles. Asthma and eosinophilia are common in Churg-Strauss, and neuropathy occurs in 65 to 75% of patients. Wegener’s granulomatosis typically results in granulomatous inflammation of the upper and lower airways and kidneys. While mononeuritis multiplex is the most common pattern of nerve involvement, neuropathy is relatively less common than in Churg-Strauss or polyarteritis nodosa. Microscopic polyangiitis may result in renal and cutaneous manifestations along with neuropathy. Compared to polyarteritis nodosa, nerve involvement likely results from damage to smaller epineurial vessels, especially those less than 40um.

**Secondary Vasculitis Syndromes**

A number of systemic disorders including connective tissue diseases, viral infections, sarcoidosis, and paraneoplastic syndromes may
cause blood vessel inflammation. Examples of connective tissue diseases that can cause vasculitis include RA, Sjögren syndrome, and SLE. Patients with these connective tissue disorders develop distal symmetrical sensory or sensorimotor axonal polyneuropathy or compression mononeuropathies more often than vasculitis-related mononeuritis multiplex. The clinical presentation of vasculitic neuropathy with connective tissue disorders is similar to that observed with primary vasculitis syndromes, with characteristic painful asymmetrical mononeuropathy, or multiple mononeuropathies. The syndrome of rheumatoid vasculitis is the best described, involving the same small to medium sized arteries affected in polyarteritis nodosa. As in most connective tissue diseases, mononeuritis multiplex due to rheumatoid vasculitis occurs in patients with established disease and is rarely a presenting symptom.

Several infections can result in vasculitic neuropathy. Most common is hepatitis C with associated cryoglobulinemia. While mixed cryoglobulinemia containing monoclonal and polyclonal immunoglobulins may be seen in association with other infections, autoimmune diseases, and lymphoproliferative disorders, it has a strong association with hepatitis C infection and may be seen in as many as 90% of patients. Neuropathy occurs in 30 to 70% of cases of cryoglobulinemic vasculitis, which affects arterioles, capillaries, and venules. Reduced complement levels and elevated antinuclear antibodies and rheumatoid factor levels are common. The painful, asymmetrical character of the mononeuropathies or multiple mononeuropathies is similar to that seen in other secondary vasculitides.

Neuropathy in HIV most commonly manifests as a distal symmetrical sensory or sensorimotor polyneuropathy. Vasculitic neuropathy is rare, usually presenting in individuals with CD4 counts between 200 to 500 cells/μL. The risk of other types of secondary vasculitis such as hepatitis B associated polyarteritis nodosa and microscopic angiitis is also increased with HIV. Rarely, vasculitic neuropathy has been reported in association with cytomegalovirus in HIV patients with CD4 counts less than 50 cells/μL.

Also reported are rare cases of Lyme disease associated vasculitic neuropathy. Some authors have demonstrated perinervitis, but not true vasculitis causing mononeuritis multiplex. The true incidence of neuropathy due to Lyme disease induced vasculitis is uncertain. In the patient of case 2, Lyme disease was an unlikely cause for her peripheral neuropathy since symptoms worsened despite adequate antibiotic therapy.

Paraneoplastic vasculitis may be seen in association with small cell lung cancer, hematological malignancies, renal cell carcinoma, and other adenocarcinomas. Patients may have detectable antineuronal nuclear antigen (ANNA-1 or anti-Hu) and CRMP-5 (also known as anti-CV2) autoantibodies. The syndrome occurs most commonly in patients with small cell lung cancer and may involve other organs in addition to peripheral nerves.

**Diagnostic Studies**

In the patient in case 2, her systemic disease did not match the features expected in primary systemic vasculitides. Hepatitis serologies indicated hepatitis B and C infections with positive hepatitis B surface antigen and hepatitis C antibodies and positive hepatitis C PCR. IgG and IgM cryoglobulins were present in the serum. Immunofixation electrophoresis showed a small IgG lambda band. A right sural nerve biopsy showed prominent chronic inflammatory cells within thickened and disrupted vessel walls. Of the secondary causes of vasculitis, the presence of mixed cryoglobulinemia with hepatitis C infection was most consistent with vasculitic mononeuritis multiplex secondary to cryoglobulinemia. The rapid progression and extensive nerve involvement eventually led to a clinical picture of relatively confluent neuropathy.

**CASE 1 EVALUATION**

The evaluation of an acquired myopathy should begin with testing to confirm a true muscle disorder. Serum CPK is often elevated and weakness should be discernable on physical examination. In patients who complain of myalgias, weakness, or fatigue, but have no CPK elevation or demonstrable weakness on physical examination, consideration should be given to nonNM disorders, such as polymyalgia rheumatic or underlying joint disease. NCS and EMG testing further help to confirm the myopathic nature of the problem and exclude neurogenic disease or defects of NM transmission. In patients who have weakness caused by muscle disease, needle EMG usually demonstrates small amplitude, short-duration, polyphasic MUAPs and early recruitment. Patients with very chronic myopathic disease, especially inclusion body myositis may also have an excess of large amplitude, polyphasic MUAPs. The identification of distinctive clinical patterns of weakness, for example, FSHD with prominent facial and shoulder girdle weakness, OPMD with bulbar weakness, or IBM with prominent finger flexor and quadriceps weakness, may provide further important clues to the diagnosis.

Once muscle disease seems reasonably certain, review of the patient’s history and medication list may reveal an obvious explanation, such as severe thyroid disease, alcohol abuse, or exposure to medications that cause myopathy such as cholesterol lowering drugs, colchicine, chloroquine, cyclosporine, amiodarone, D-penicillamine, or chronic steroid therapy. Blood work to look for elevated inflammatory markers or systemic diseases associated with myopathy should be considered (Table 1).

Muscle biopsy is an important component of the evaluation and in cases of suspected inflammatory myopathy is best performed before the initiation of treatment. In the case of DM, the classic feature is perifascicular atrophy. This finding may not be seen on all specimens due to the patchy involvement of the disease, but inflammatory infiltrates consisting of macrophages, B lymphocytes, and CD4+ T cells are also found in the perimysium and endomysium of scattered necrotic fiber. Small blood vessels of involved muscle have deposits of complement components, immunoglobulin M and G, and membrane attack complexes. PM specimens demonstrate fiber size variation with scattered necrotic and regenerating fibers. Even in nonnecrotic regions of muscle, prominent endomyositis inflammatory infiltrates consisting of activated CD8+, alpha and beta T cells, macrophages, and plasma cells are seen. In IBM, the key
findings are muscle fibers containing rimmed vacuoles lined with granular material, endomyosal inflammation consisting of CD8+ T cells and macrophages, and tubulofilamentous inclusions on electron microscopy. As in PM, inflammatory infiltrates may be present even in nonnecrotic muscle fibers. Amyloid deposition may also be seen within muscle fibers. Myositis with other connective tissue diseases may have features of a microangiopathy similar to DM or may have an appearance of PM. In sarcoid myopathy, noncaseating granulomas consisting of Langhans giant cells, epithelioid histiocytic cells, and lymphocytes, are the classic finding. Macrophages and lymphocytes are also commonly seen, lymphocytes in areas surrounding granulomas and macrophages within the granulomas themselves.

Table 1 Recommended testing to evaluate inflammatory myopathies and vasculitic neuropathies

<table>
<thead>
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<th>Suggested blood work</th>
<th>Inflammatory myopathy</th>
<th>Vasculitic neuropathy</th>
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<tr>
<td>Complete metabolic panel</td>
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</tr>
<tr>
<td>Complete blood count</td>
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</tr>
<tr>
<td>HIV antibodies</td>
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<td>+/-</td>
</tr>
<tr>
<td>Thyroid stimulating hormone</td>
<td>+</td>
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</tbody>
</table>

HIV = human immunodeficiency virus

CASE 2 EVALUATION

In the case of vasculitic neuropathy, the evaluation strategy initially depends on correctly identifying the clinical syndrome and confirming multifocal neuromyopathies on EDX testing. NCSs may initially demonstrate pseudo conduction block in segments of nerve with focal ischemic damage, but within 10 days, the segment of nerve distal to ischemia degenerates. Typical electrophysiological indications of axonal damage (fibrillations, positive sharp waves, reinnervation changes) appear as expected over subsequent weeks and months.

As with inflammatory myopathies, histological confirmation of peripheral nerve vasculitis is important because chronic immunosuppressive treatment is usually required. Unfortunately, due to the patchy character of vascular inflammation, nerve and muscle biopsy may only have 60% sensitivity, if the most rigid criteria of inflammation and vessel wall destruction are used. Other features such as multifocal nerve fiber loss and immune complex deposition may also be observed. In polyarteritis nodosa, the involvement of larger arteries may permit diagnosis by angiography. Other laboratory tests (Table 1) help confirm the inflammatory nature of the disorder and allow more specific characterization of the syndrome.

CASES 1 AND 2 TREATMENTS

Limited randomized, controlled, prospective clinical trial data exist for the treatment of inflammatory myopathies. Corticosteroids, azathioprine, methotrexate, cyclophosphamide, chlorambucil, cyclosporine, mycophenolate mofetil, and intravenous gammaglobulin infusion have all been described for the treatment of PM and DM. Initial treatment with corticosteroids is advocated by most experts. The addition of one of the other agents such as methotrexate or azathioprine is often helpful as an adjunctive treatment and may permit lowering of the corticosteroid dose. These medications require regular monitoring and side effects are common. Most patients respond at least partially. IBM is typically refractory to immune modulating treatments. Sarcoid myopathy also has limited clinical treatment trial data, but similar to PM and DM, the use of steroids, azathioprine, methotrexate, and mycophenolate mofetil have all been described. These treatments have been reported to have good results in some patients with sarcoid myopathy, but others have had more resistant disease.

should have annual testicular and prostate examinations. Chest, abdominal, and pelvic computed tomographic imaging, colonoscopy, mammogram, and blood work including a CBC, hepatic function panel, and routine chemistries should be considered. Physicians should also be vigilant for other systemic accompaniments of DM such as interstitial lung disease, cardiac conduction defects, dysphagia or delayed gastric emptying, arthritis, and signs of associated vasculopathy. In PM, cardiac and pulmonary manifestations may be similar to those in DM. In contrast, IBM is not associated with myocarditis or interstitial lung disease. The systemic manifestations of sarcoidosis are numerous. Pulmonary, cardiac, ocular, renal, and hepatic involvement can all occur in conjunction with muscular involvement.
Treatment of vasculitic neuropathies depends on the underlying cause. Immunosuppression is usually helpful in the setting of systemic vasculitis or when neuropathy is associated with underlying connective tissue disease. In part because these syndromes are relatively uncommon, definitive randomized, controlled, prospective treatment data are lacking. Corticosteroids, cyclophosphamide, methotrexate, azathioprine, and mycophenolate mofetil all have all been used. Corticosteroids are widely used as a first line treatment. Among the other agents, cyclophosphamide may be relatively more efficacious but has significant toxicities.

In the case of vasculitic neuropathy due to an infectious cause, the key is identification and treatment of the underlying infection rather than immunosuppression. Patients with hepatitis C and cryoglobulinemic neuropathy usually benefit from pegylated interferon α-2a or 2b or ribavirin, though pegylated interferon itself has been a reported cause of neuropathy. In some cases, a short course of immunosuppression is warranted, for example, in patients with hepatitis B associated polyarteritis nodosa. However, the use of immunosuppression must be weighed against the risk of increased viremia.

**CASE 3 DESCRIPTION**

**History**

A 48-year-old woman noted weakness of the legs which progressed slightly over the prior week. She also noted occasional muscle cramping and mild myalgias. The day prior to admission she noted difficulty arising from a chair and could not climb stairs. She was admitted to the hospital when she became suddenly much weaker. Upon awakening on the day of admission she noted difficulty walking and by midday was no longer able to walk and could not raise her arms over her head. She continued to become weaker until she was unable to move her limbs at all. She reported no sensory disturbance, confusion, dyspnea, dysphagia, diplopia, or pain other than mild myalgias. She had no prior history of similar events and no family history of neuromuscular disease or other pertinent medical problems. She had not been recently ill. She remained able to speak even when profoundly weak. Her past medical history included three routine pregnancies. She was noted to be hypothyroid 8 years ago and has been on stable levels of hormone replacement. She has been experiencing irregular menses, hot flashes, and modest mood swings for the past 2 years.

On examination, she was lying quietly in bed with eyes open. Her voice was soft, but only slightly dysarthric. Heart rhythm was regular and heart rate and blood pressure were normal. She was afebrile. There were no cervical bruits. Respiration was regular at 16/min. She was fully alert and followed commands briskly with her eyes, but was unable to move her arms or legs. Facial strength was mildly reduced but symmetric. Extraocular movements were full and there was no nystagmus. Sensory examination revealed no loss of pin, temperature, or vibratory perception. Muscle tone was reduced and reflexes were absent in all limbs.

**DIFFERENTIAL DIAGNOSIS**

Table 2 includes a variety of disorders to be considered when faced with acute to subacute generalized weakness. One can typically use features of the clinical history and examination to narrow the differential considerably. Weakness due to an abnormality in the brain typically is accompanied by alterations of consciousness and sensory perception as well as oculomotor deficits in the setting of brainstem dysfunction. A lesion in the cervical spinal cord often is accompanied by a sensory level and perhaps by bowel and bladder dysfunction. Cerebral and cranial nerve function should be entirely normal with a spinal cord lesion. Neuropathy of sufficient severity to account for widespread generalized weakness will nearly always be associated with abnormalities of sensory perception as well. The subtype of Guillain-Barré syndrome known as acute motor axonal neuropathy is a notable exception. Disorders of neuromuscular transmission and of muscle will result in purely motor abnormalities. The most common defect in neuromuscular transmission,
myasthenia gravis, nearly always produces bulbar and oculomotor abnormalities when severe enough to produce generalized weakness. An elevated serum creatine phosphokinase (CPK) level is found in many disorders of muscle, but a normal level does not preclude localization to the muscle. Intoxication most often results in alteration of consciousness. Critical illness neuromyopathy is an example of a disorder to be considered only under very specific circumstances. Electrolyte disturbances are typically identified on routine laboratory testing (the common “chemistry panel”).

**EVALUATION**

Urgent magnetic resonance imaging studies of the brain and cervical spine revealed no important lesions. Routine chemistry panel revealed a markedly reduced potassium level of 1.8 mMol/L (normal 3.5-5). Thyroid function studies were normal. NCSs revealed normal sensory responses in the right arm and leg. Motor NCSs revealed absent responses in the legs and markedly reduced CMAP amplitude with stimulation of the right ulnar and median nerves (0.1 and 0.3 mV, respectively). Needle examination revealed reduced insertional activity and no voluntary motor units in limb muscles. Electrocardiogram revealed flattening of the T-waves and the presence of small U-waves.

**DISCUSSION**

The development of profound limb weakness with relative sparing of bulbar and respiratory muscles is typical of periodic paralysis. The absence of sensory abnormalities and preserved sensorium are also cardinal features of periodic paralysis. Most cases of periodic paralysis are due to genetic abnormality in an ion channel which results in episodes of electrical failure in the muscle membrane. This electrical failure results in markedly reduced CMAP amplitudes on NCSs, the hallmark of periodic paralysis during an attack of weakness.

Periodic paralysis is often divided into hyperkalemic and hypokalemic forms. Familial hyperkalemic periodic paralysis is caused by a mutation of the sodium channel gene on chromosome 17q. In this disorder, episodic weakness accompanied by increased serum potassium levels begins in childhood. The episodes of weakness are typically relatively mild. Myotonia is typically present on needle examination even when weakness is not present.

Familial hypokalemic periodic paralysis is caused by a mutation in either the calcium channel on chromosome 1q or the sodium channel on chromosome 17q. The episodes of paralysis are often severe. Potassium levels are often reduced, but may be normal during attacks of weakness. Routine EMG and NCSs are typically normal between attacks of weakness, and reveal markedly reduced CMAP amplitudes during attacks. Needle examination during an attack often reveals decreased insertional activity given the muscle membrane inexcitability.

Andersen-Tawil syndrome is another form of periodic paralysis in which affected patients have characteristic mild dysmorphic features and cardiac conduction defects. Short stature, micrognathia, arched palate, low-set ears, broad nose, and short index finger are common physical attributes of this disorder. Prolonged QT interval is the most common cardiac conduction abnormality. This disorder is caused by a mutation in the inward rectifying potassium channel gene on chromosome 17. There is no associated myotonia, and potassium shifts and serum potassium levels are inconsistent during attacks.

It is important to note that periodic paralysis can occur as an acquired disorder in the setting of profoundly reduced potassium levels. Potassium levels may be reduced by severe losses, such as seen with severe diarrhea, by an intrinsic renal abnormality, or by transcellular shifts in potassium. In the case presented here, additional testing revealed that the patient suffered from previously undiagnosed renal tubular acidosis. Other situations in which periodic paralysis may develop include thyrotoxicosis and barium intoxication.

**TREATMENT**

The patient received intravenous potassium replacement and rapidly regained strength. Within 24 hours, the patient was walking. Oral maintenance replacement of potassium will be necessary. Further evaluation of the renal tubular acidosis by a renal specialist is also appropriate. On the day following hospital admission, when the patient had regained near normal strength, NCSs were repeated. The CMAP amplitudes in the right arm and leg were now normal. Needle EMG examination also was normal.

**CASE 4 DESCRIPTION**

**History**

A 65-year-old man was referred for evaluation of difficulty walking. He first noted difficulty arising from a chair and exiting his car 4 months prior to evaluation. The weakness slowly progressed to include weakness of his shoulders and now causes difficulty with ambulation even on level ground. He reports a moderate degree of muscle soreness and reports that his legs feel stiff. He frequently cramps in overly-active muscles. He notes a profound sense of fatigue and is unable to work in his garden. He reports no numbness, tingling, or apparent loss of sensation in his hands or feet. He has not noted any visual problems, dysarthria, or dysphagia. He is sleeping well and notes no shortness of breath. He notes an occasional problem with short-term memory and feels “in a fog” at times.

**Neurologic Examination**

Mild abnormalities of short-term memory are apparent. Ocular alignment is normal and there is no ptosis. The face is symmetric with normal strength. Facial sensation is normal. The tongue is without...
atrophy or fasciculation and protrudes midline. The palate elevates symmetrically. Hearing is intact. Neck flexion strength is normal, but there is 4+/5 weakness of neck extensors. Testing of limb strength reveals symmetric proximal >distal weakness: MRC grade 4 is noted in the deltoid and infraspinatus muscles, 5- in the biceps and triceps muscles, and 5 in distal muscles of the upper extremities. In the legs, MRC is 3+ in hip flexors, 4 in quadriceps, and 5- in other leg muscles. Sensory examination reveals normal perception of cold, pin, vibration, and joint position. Reflexes are brisk and symmetric with spread in the arms, and brisk in the legs with crossed adduction with patellar reflex percussion. Plantar responses are flexor. He cannot arise from a chair without using his arms. Spontaneous gait is wide-based and has a “waddling” quality.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of slowly progressive generalized weakness is extensive and contains disorders of the entire motor unit as well a variety of medical disorders which include weakness as a primary manifestation. The lack of sensory involvement in this case removes the most common forms of polyneuropathy from the differential. If the weakness in this case is caused by denervation, the disorder is one selectively affecting the anterior horn cell, motor root or motor axon. The combination of progressive generalized weakness and hyperreflexia seen in this case makes amyotrophic lateral sclerosis (ALS) feature prominently in the differential diagnosis. The pattern of symmetric proximal weakness with myalgia is atypical of ALS, however. Disorders of impaired neuromuscular transmission also are to be considered seriously in this differential diagnosis. The lack of bulbar or ocular signs or symptoms is unusual for myasthenia gravis. Lambert Eaton myasthenic syndrome (LEMS), a presynaptic defect in neuromuscular transmission caused by antibodies to the motor nerve terminal calcium channel, often presents with leg weakness, but reflexes are typically reduced in this disorder. Symptoms of autonomic dysfunction, such as orthostatic hypotension and impotence, often accompany weakness in LEMS. A myopathy is a classic cause of progressive proximal weakness. The presence of myalgias in this case is also consistent with a disorder of the muscle. Serum CPK and/or aldolase levels are often elevated in myopathies, but a number of myopathies produce considerable weakness with normal to minimally elevated CPK/aldolase levels. Reflexes are typically normal to slightly reduced in myopathic disorders. Inflammatory myopathies, toxic myopathies, and even late onset congenital myopathies or muscular dystrophies are possibilities in this case. Muscle dysfunction associated with medical illness should also be considered. Hypothyroidism, hyperparathyroidism, hypokalemia, hypermagnesemia, hypo- and hypercalcemia, Cushing syndrome, and adrenal insufficiency are relatively common medical conditions associated with muscle weakness. The presence of cancer should be considered, particularly elderly patients, presenting with generalized weakness. A number of recognized paraneoplastic syndromes cause weakness. These are likely autoimmune disorders in which the immune system's response to cancer “spills over” and recognizes antigens on nerve, muscle, the neuromuscular junction, or the central nervous system. Alternatively, some forms of cancer may produce compounds which mimic hormone action and create a syndrome of hormone excess. Paraneoplastic syndromes affecting essentially the entire motor system have been described. In addition, fatigue and weakness is often present in patients with cancer in the absence of a demonstrable antibody or other evidence of autoimmunity. This has been termed asthenia of cancer, and its mechanism is poorly understood.

EVALUATION

The routine chemistry battery revealed normal serum sodium, potassium, and chloride levels, hepatic and renal function, but the serum calcium level was mildly elevated at 11.9 mg/dl. Serum CPK level was normal at 135 IU/l. Thyroid-stimulating hormone was normal. No paraneoplastic antibodies were detected. Acetylcholine receptor antibodies and anti- muscle-specific kinase antibodies also were not present.

EDX studies were performed. Sensory and motor NCSs in the right arm and leg were normal. No decrement was noted on repetitive stimulation. Needle examination revealed reduced recruitment of polyphasic, moderately large units in the weakest, proximal muscles. No abnormal spontaneous activity was noted.

Because of the elevated serum calcium level, parathyroid hormone level was measured and was found to be elevated at 95 pg/ml, indicative of hyperparathyroidism. The patient's weakness and recent memory disturbance is likely to be related to this finding.

DISCUSSION

Many of the medical conditions which are commonly associated with generalized weakness are apparent on routine laboratory studies. For example, potassium and calcium levels are typically determined on the routine chemistry panel obtained in almost every patient. As demonstrated in the prior case, profound hypokalemia can cause severe weakness. In contrast, relatively subtle hypercalcemia can be an indicator of hyperparathyroidism. Parathyroid hormone levels should be checked in any case of weakness with demonstrated hypercalcemia, or when other systemic features such as unusual bone loss, confusion, nausea, or recent kidney stones are noted. In this case, the patient did have mild confusion and memory loss, a clue that the weakness was a feature of a systemic disorder. Hyperparathyroidism has been proposed as a prominent mimic of ALS. Reflexes can be somewhat increased in hyperparathyroidism, and of course hyperreflexia is a hallmark of ALS. However, the weakness in hyperparathyroidism tends to be symmetric and proximal, an unusual pattern for ALS. In addition, EMG in hyperparathyroidism typically reveals relatively subtle findings, not the prominent widespread active and chronic denervation typically detected in patients with ALS. A recent report of patients who meet formal criteria for ALS and have hyperparathyroidism indicates that treatment of the hyperparathyroidism does not alter the course of the disease, and that the conditions were likely coincidental in this population.
TREATMENT

Primary hyperparathyroidism is most commonly caused by hypersecretion from a solitary parathyroid adenoma. Secondary hyperparathyroidism results from conditions which cause hypocalcemia such as severe calcium deficiency, severe vitamin D deficiency, and renal failure. Parathyroid hyperplasia or malignant parathyroid tumors may also cause primary hyperparathyroidism. Nuclear 99mTc-sestamibi scanning is the most sensitive imaging modality for such adenomas, and may be supplemented with parathyroid ultrasound. Surgical removal of the affected parathyroid gland is the definitive treatment. Nonsurgical ablative therapy may be an option for patients who are not surgical candidates, but it is not as effective as surgical therapy. Effective treatment of hyperparathyroidism usually results in complete resolution of neuromuscular and other neurologic symptoms.5, 10, 11, 17

REFERENCES for Cases 1 & 2

REFERENCES for Cases 3 & 4


CASE DESCRIPTION

A 79-year-old left-handed white male presented with a lifelong history of episodic muscle stiffness and weakness. His symptoms began at age 4, causing difficulty with ambulation, use of his hands, as well as opening his eyes or lips in cold conditions. Symptoms progressed in severity and frequency over 15 to 20 years. Stiffness eventually involved his face, forearms, arms, hands, thighs, legs, as well as the tongue and eyelids with minimal progression afterwards. The major triggers for stiffness included: cold weather, continued activity, and emotional stress. Symptoms were relieved with rest and warmer temperatures. He also experienced episodes of weakness in his arms, forearms, hands, thighs, legs, and muscles of mastication that would last minutes to hours. Weakness was primarily induced by cold weather or with continued use of his limbs after the onset of stiffness, but could also occur spontaneously. He had developed fixed and mildly progressive weakness in his hands and thighs for over 8 to 10 years. The patient occasionally experienced difficulty swallowing food in cold weather and had difficulty swallowing cold beverages.

No dietary triggers or effects related to any medication were noted. He did not complain of muscle cramps, myalgia, cola-colored urine, palpitations, shortness of breath, or of changes in sensation, vision, balance, bowel, or bladder function.

Past medical history was positive for hypertension and prostate adenocarcinoma, status post-radiation therapy. Medications included lisinopril and multivitamins.

Family history was significant for similar symptoms of stiffness and weakness in his paternal grandmother, father, brother, sister, son, daughter, two nephews, and a granddaughter.

EXAMINATION

The general examination was normal. In particular, there was no frontal balding, skin rash, cataracts, or skeletal abnormalities. A cognitive examination was normal. Cranial nerve examination was normal except for lid lag and eye closure myotonia that worsened with repetition (paramyotonia) and minimal (5-/5) neck flexor weakness. Motor testing demonstrated mild hypertrophy in the biceps, deltoids, and paracervical spinal muscles, and mild atrophy in the forearm muscles. There was grip myotonia that worsened with repetition (paramyotonia) in the absence of percussion myotonia. Muscle tone and strength were normal except for deep finger flexors and thumb flexors and wrist flexors 4+, finger extensors 4+, hip flexors 4+ to 5-. Coordination, deep tendon reflexes, and sensory examination were normal, and there was no rigidity in the limbs, cog wheeling, or tremor. Gait and stance were normal with the exception of stiffness in the proximal thigh muscles that remained unchanged with continued ambulation.

PREVIOUS WORKUP

Normal results were noted for serum electrolytes, creatine kinase (CK), thyroid-stimulating hormone (TSH), blood urea nitrogen, creatinine, complete blood count (CBC), and erythrocyte sedimentation rate. Previous electromyography (EMG) reported widespread myotonic discharges. No muscle biopsy had been performed.
Differential Diagnosis

The patient is a 79-year-old man with a chronic course of muscle stiffness and episodic weakness. The most helpful features in this presentation are paramyotonia and episodes of weakness that are most sensitive to cold and activity, an autosomal dominant family history, evidence for paramyotonia on examination, and myotonic discharges on EMG.

Myotonic Disorders

Myotonic disorders may be classified under the larger group of muscle channelopathies and are generally divided into dystrophic and nondystrophic forms, although the distinction between the two groups is not always clear. Each group can be further subdivided based on the type of channel involved and presenting features (Table 1). Some myotonic disorders are accompanied by episodic (e.g., paramyotonia congenita) or fixed (e.g., myotonic dystrophy type 2) weakness, whereas others (e.g., myotonia fluctuans) do not present with weakness. Some are sensitive to dietary triggers such as potassium (e.g., potassium sensitive periodic paralysis) or cold (e.g., paramyotonia congenita).

Myotonia is the delayed relaxation seen in skeletal muscle following contraction that could occur in various muscles, but is most markedly noticed in the eyelids, mouth, hands, and is also characterized by stiffness in the proximal thighs. It usually improves or abates after repeated muscle activity; the so-called “warm-up phenomenon.” Paramyotonia (paradoxical myotonia) also refers to delayed relaxation of skeletal muscle following contraction; however, here the symptoms worsen with repeated activity. In both cases, the electrophysiological equivalent of these findings are myotonic discharges seen on needle EMG. These are represented by spontaneous firing of muscle fiber action potentials as runs of positive waves or brief spike potentials (20 to 150 Hz) that typically vary in frequency and amplitude. They may be induced by needle insertion and movement, muscle percussion, or voluntary contraction. It is important to keep in mind that other conditions may demonstrate myotonic discharges on needle EMG. These may include certain drugs (e.g., cholesterol lowering agents, cyclosporine, chloroquine, and colchicines), Pompe disease, inflammatory myopathies, and even chronic denervation (usually as brief runs of positive sharp waves).

The workup of myotonic disorders may include laboratory tests such as serum electrolytes, CK and TSH; electrophysiological studies, in particular needle EMG, the short and prolonged exercise studies (outlined in detail in articles by Fournier and associates), and genetic testing. With the availability of genetic testing, muscle biopsy and challenge tests (e.g., inducing hyperkalemia) are not used as often now as they were in the past.

In regards to management, various medications such as anti-epileptic drugs (phenytoin and carbamazepine), and antiarrhythmic drugs (mexiletine and procainamide) have been used to reduce stiffness. Acetazolamide has been used to treat episodic weakness with various degrees of success (none are approved by the Food and Drug Administration for therapy). Dietary management to minimize triggers, physical therapy, exclusion of obstructive sleep apnea, evaluation for and treatment of systemic abnormalities (e.g., cardiac and pulmonary issues in myotonic dystrophy type 1), attention to swallowing, and to the increased risk for general anesthesia (e.g., malignant hyperthermia in some) are of utmost importance.

Myotonic Dystrophies

Myotonic dystrophies are inherited in an autosomal dominant fashion, in addition to myotonia, they present with progressive muscle weakness, multi system involvement, and early development of cataracts. They are currently classified into myotonic dystrophy type 1 (DM1) and type 2 (DM2), also called proximal myotonic myopathy (PROMM). Their pathogenesis is related to an expansion of tandem repeats (CTG repeats on the DMPK gene in DM1 and CCTG repeats on the ZNF9 gene in DM2), resulting in toxic gain of function of the mutant ribonucleic acid (RNA) and sequestration of RNA binding proteins.

DM1 is the most prevalent form of muscular dystrophy in adults with an incidence of 13.5 per 100,000 live births. It seems to increase in severity and occur at an earlier age in successive generations (anticipation) and with maternal bias (more marked expansion of the CTG repeat in children of mothers with DM1). It could occur at any age with its most severe form occurring at birth (congenital DM) with generalized hypotonia and severe weakness, facial diplegia (tent-shaped mouth), mental retardation, gastrointestinal tract involvement, respiratory insufficiency, and early death. DM1 may also present as a milder phenotype with myotonia, frontal balding, cataracts (posterior subcapsular and multicolored lens opacities), and a normal lifespan. In addition to the symptoms seen in mild forms, the classical form includes muscle weakness and wasting, cardiac conduction abnormalities, physical disability, and a shortened lifespan. It more typically presents with early neck flexor and distal limb weakness and atrophy (wrist and finger extensors and ankle dorsiflexors), jaw and facial muscle involvement (ptosis and drooping mouth), as well as dysarthria and dysphagia. The patients may have cognitive and behavioral issues. Early referral to cardiology is of vital importance, as there may be a need for early therapy in patients with cardiac conduction defects and automatic implantable cardioverter defibrillator placement. Exclusion of obstructive sleep apnea and its treatment are also important in the prevention of pulmonary hypertension and cor pulmonale.

Although the incidence of DM2, or PROMM, is uncertain, it could be as high as that of DM1. It does not seem to have the anticipation and maternal bias seen in DM1, and congenital forms have not been described. While it may occur in childhood, its onset is usually between 20 and 60 years of age. It usually presents with complaints of intermittent stiffness and pain in the thigh muscles or progressive proximal weakness. It may materialize or worsen during pregnancy, and could initially fluctuate or transiently improve. As compared with DM1, the weakness and atrophy are more in proximal than distal limb muscles (neck flexors, elbow extensors, hip flexors, and knee extensors), and manual skills remain...
largely intact. One of the interesting features in DM2 is pain that may be episodic and described as disabling, burning, tearing or jabbing, reported mostly in the thighs, shoulders, and upper arms, or presenting as peculiar chest pains leading to multiple negative cardiac evaluations. The cognitive and systemic issues described for DM1 may also be present, but are generally milder. Due to the wide spectrum of presenting features, there should be a high suspicion for DM2, and none of the common clinical key features (proximal weakness, myotonia, cataracts, elevated CK values, or established family history) is absolutely mandatory.11

Myotonic dystrophies usually present with normal or mildly elevated serum CK. Electrophysiological studies demonstrate normal nerve conduction studies (NCSs), myotonic discharges on needle EMG,10 fibrillation potentials (FP), positive sharp waves (PSW), and myopathic motor unit action potentials (MUAPs) in weak muscles. Muscle biopsy shows abundant internalized nuclei, ring fibers, increased connective tissue (in dystrophic muscle), occasional sarcoplasmic masses, and type 1 fiber atrophy (in DM1). Genetic testing is commercially available for both DM1 and DM2.

Therapy may include the use of mexiletine for myotonia (especially in DM2), which is painful. It may be started at a dose of 150 mg twice daily and slowly increased (maximum of 300 mg three times daily). CBC, serum electrolytes, renal and liver function and electrocardiogram (EKG) need to be performed at baseline and periodically thereafter. It should be used with caution in patients with DM1, and it may be beneficial to request cardiology clearance before starting therapy.
The combination of progressive proximal thigh weakness, hand weakness, and myotonia seen in this patient may raise the concern for myotonic dystrophies; however, the mild degree of weakness in comparison to myotonia, absence of cataracts, frontal balding, temporal wasting, and systemic involvement greatly reduced the chance for DM1. While DM2 could always be considered, it does not usually present with this degree of cold sensitivity and periodic attacks of weakness.

**Chloride Channel Mutations**

**Myotonia Congenita**

As a group, myotonia congenita (MC) disorders are due to mutations in the muscle chloride ion channel, CLCN1 gene on chromosome 7q35. The reduction in chloride conductance leads to uncontrolled bursts of action potentials and results in myotonic discharges.

Dominant MC (Thomsen Disease) is inherited in an autosomal dominant pattern with varying severity among family members. It is usually noticed in the first 2 years of life with difficulty in opening the eyes, facial distortion after a crying spell, leg stiffness with the first few steps, and occasional falls. Older patients complain of muscle stiffness that may cause functional limitations but minimal weakness. This presents in the limbs, face (particularly the eyelids and lips), muscles of mastication, and is noticed with a difficulty in swallowing. The typical “warm-up” phenomenon is described as well as the return of symptoms following a brief period of rest. With the exception of generalized muscle hypertrophy, action (eyelids and hands) and percussion (thenar eminence and extensor digitorum communis) myotonia, patients have a normal examination. It does not cause systemic disorders, and patients have a normal lifespan.

Recessive MC (Becker Disease) is inherited in an autosomal recessive pattern. Age of onset is usually 4 to 12 years, with a gradual increase in symptoms during the first 2 decades. It shares many of its features with the dominant form, but has a few notable differences. The myotonia in the recessive forms is more severe, mostly present in the lower limbs, and is more proximal than distal. Patients may have transient muscle weakness following a severe bout of myotonia, especially in the distal upper limb muscles, and may develop mild fixed weakness in time. Recessive MC does not cause systemic disorders, and patients have a normal lifespan.

Patients with MC usually have normal or slightly elevated serum CK (often higher in recessive forms). Electrophysiological studies demonstrate NCSs and widespread myotonic discharges which may prevent accurate determination of MUAP morphology. The short exercise study demonstrates mild decrease in compound muscle action potential (CMAP) amplitude following exercise with recovery over 1 to 2 minutes, and increased decrement with repetition. This pattern in CMAP amplitude is also seen with repetitive nerve stimulation (RNS) at 10 Hz or more (greater decrement at higher frequencies). Muscle biopsy may only demonstrate mild increased variability in fiber size and central nuclei. Genetic testing is commercially available for both forms of MC.

**Sodium Channel Mutations**

Most patients with MC do not require therapy; however, mexiletine may be used in patients with severe myotonia that limits function.

The presenting features of paramyotonia, significant cold sensitivity, and episodic weakness reduce the chance for the diagnosis of MC in this patient.

The potassium aggravated myotonias (PAMs) demonstrate sensitivity to the intake of potassium and myotonia in the absence of muscle weakness. They may exhibit various degrees of paramyotonia in the eyelids in between the attacks. Patients with myotonia fluctuans report having “good days” (symptom free) and “bad days” with delayed onset of myotonia several minutes after exercise, involving the limbs, extraocular, and masticatory muscles. Myotonia permanens presents as a severe form of myotonia fluctuans in which patients have constant myotonia worsened by potassium and exercise. Acetazolamide responsive myotonia presents as painful muscle stiffness in childhood that worsens with age into early adulthood and is most severe in the face and hands. It is provoked to a lesser extent by exercise.

Serum CK may be normal or slightly elevated in the PAMs. Electrophysiological studies demonstrate myotonic potentials on needle EMG (especially after exercise) with normal MUAPs. Routine NCSs and both the short and prolonged exercise tests are normal at room temperature (may look like MC or PMC patients with cooling). Muscle biopsy shows nonspecific changes. Genetic testing is commercially available.

In addition to avoidance of potassium intake, the myotonia in PAM may respond to therapy with mexiletine. Acetazolamide responsive myotonia is particularly responsive to acetazolamide.

**Potassium Sensitive Periodic Paralysis**

Potassium sensitive periodic paralysis (HyperPP) usually manifests in the first decade of life with relatively short (usually less than 2 hours) attacks of weakness, mostly occurring in the morning (can occur at any time), and is precipitated by rest following exercise, fasting, intake of potassium rich food, stress, and fatigue. The onset of an attack is often heralded by paresthesia and a “sense of heaviness” in the legs or small of the back that leads to weakness in thighs and calves and then progresses to other muscle groups (generalized and even affecting bulbar and respiratory muscles).
The weakness remains mainly focal and may be postponed or prevented by mild exercise. Sensation and sphincter control are unaffected. Patients may have pain in the affected muscles for a few days after an attack. Attack frequency is highly variable (several times a day to once a year) and often decreases with age. Patients may have lid lag or eyelid myotonia between the attacks and some develop fixed weakness (mostly proximal) in time. While most patients present with episodic attacks of weakness, some may also demonstrate myotonia or paramyotonia, mostly in the eyelids, tongue, and hands, along with percussion myotonia in the extensor digitorum communis muscle and thenar eminence.

While serum potassium may be elevated (5 to 6 mEq/L) during an attack, it may remain normal, with even possible transient hypokalemia after the attack. Serum CK may be normal or mildly elevated. Electrophysiological studies demonstrate normal nerve conduction studies between the attacks. Needle EMG may show increased insertional activity, FP and PSW (signs of muscle hyperexcitability and not denervation), along with myotonic discharges in the group of patients with clinical myotonia. MUAP morphology and recruitment patterns are normal except for the appearance of myopathic MUAPS in muscles that show fixed weakness. During the course of an attack, CMAP amplitude progressively declines, and needle EMG may show MUAPS that are decreasing in number and amplitude then progress to complete electrical silence with paralysis. The short exercise study demonstrates an increase in CMAP amplitude following exercise that increases with repetition. Prolonged exercise testing shows transient increase in CMAP amplitude post exercise with progressive reduction in amplitude after approximately 10 to 20 minutes. Muscle biopsy is mainly nonspecific, except for the occasional presence of vacuoles. Genetic testing is commercially available.

Prophylactic therapy includes an avoidance of triggers, treatment with acetzolamide (125 to 1000 mg daily in divided doses), and a high carbohydrate diet. Mexiletine may be used if patients have severe myotonia. The attacks are usually short lived and do not require therapy. Simple carbohydrates (e.g., fruit juice), and beta adrenergic agonists (albuterol and salbutamol in the absence of cardiac arrhythmias) may be used. Rarely, severe attacks may need treatment with intravenous glucose, insulin, or calcium carbonate (especially in patients with EKG abnormalities). One should always consider the possibility of over treatment and post-attack hypokalemia, and therapy should be performed under cardiac monitoring.

**Normokalemic Periodic Paralysis**

Normokalemic periodic paralysis patients are similar to those with HyperPP in most aspects including a sensitivity to potassium; however, the serum potassium levels are normal during attacks.

**Paramyotonia Congenita**

Paramyotonia congenita (PMC) and HyperPP are allelic disorders with some kinships having clinical features of both. PMC usually manifests within the first decade of life with myotonia and attacks of weakness (in some patients) that are induced by exercise, cold, or an intake of potassium. Mothers may report infants that are unable to open their eyes after a crying spell or have facial spasm after washing with cold water. Patients may complain of hand stiffness while shoveling snow, or while in the frozen food section of the supermarket. The attacks of weakness are mostly focal, but may become generalized, causing flaccid paralysis. They occur in the face, hand, pharyngeal, and tongue muscles, and can last for several hours. Pain is not a common complaint and the symptoms may remain stable or improve slightly with age.

During attacks, serum potassium levels may be normal or elevated, and serum CK is normal or mildly elevated. Electrophysiological studies demonstrate normal nerve conduction studies between the attacks. Needle EMG shows myotonic discharges. The cooling of muscle results in dense fibrillation like potentials with gradual reduction in MUAP activity until disappearance of electrical myotonia, leading to complete electrical silence (after paralysis). In patients presenting with pure paramyotonia, cooling only results in increased myotonic discharges. The short exercise study demonstrates reduced CMAP amplitude following exercise that does not repair to baseline levels and worsens with repetition. Prolonged exercise testing results in a severe reduction in CMAP amplitude post exercise that does not return to baseline over the next 30 to 40 minutes. Cooling causes further decline in CMAP amplitude in the short exercise test. Muscle biopsy demonstrates nonspecific changes with vacuoles and tubular aggregates in some patients with episodic weakness. Genetic testing is commercially available.

Mexiletine may be used to prevent muscle stiffness and weakness associated with cold, while acetazolamide can be used for reducing the periodic attacks of paralysis.

Due to the presence of paramyotonia, cold sensitivity and episodic weakness, the diagnosis of a sodium channelopathy, PMC in particular, is reasonable for this patient.

**Schwartz-Jampel Syndrome Chondrodystrophic Myotonia**

Schwartz-Jampel syndrome chondrodystrophic myotonia (SJS) is a rare autosomal recessive disease (autosomal dominant forms are also reported) that is divided into types 1 and 2. Type 1A, which demonstrates both muscle and skeletal involvement, has been related to mutations of HSPG2 gene on chromosome 1p35-36.1. This gene encodes for perlecan which is a large multifunctional protein that is secreted into the basement membranes. Patients usually present in infancy with dysmorphic faces (including micrognathia, blepharophimosis, low set ears, and pursed lips with a small mouth), shortened stature, bowing of the femur and tibia, pectus carinatum, decreased suck, weak high pitched cry, myotonic contractions of facial muscles with crying, delayed developmental milestones, and stiff and slow movements with a waddling gait.

Serum CK is normal or mildly elevated, and skeletal imaging shows osteochondrodysplasia. Electrophysiological studies demonstrate normal routine NCSs. Needle EMG demonstrates continuous electrical activity which includes myotonic discharges (may not always be the typical waxing and waning pattern), complex repetitive discharges, and myokymic discharges. Muscle biopsy demonstrates decreased perlecan staining. Mutation screening may prove laborious.
FURTHER DIAGNOSTIC WORKUP

EDX testing performed on the patient indicated widespread myotonic discharges that worsened in the presence of cold temperatures. Short exercise testing (Figure 1) demonstrated reduced ulnar abductor digit minimi CMAP amplitudes postexercise that worsened with repetition and in the presence of cold temperatures. It also indicated reduced CMAP amplitude post prolonged exercise (Figure 2) that did not return to baseline for over 20 minutes. Since these findings were consistent with that reported for patients with PMC, and due to clinical suspicion, the patient was tested for sodium channel SCN4A mutations and was found to have a T1313M mutation previously reported in families with PMC.

![Short Exercise Test Ulnar-ADM](image1)

**Figure 1** Short exercise test measuring the right ulnar-ADM CMAP

![Long Exercise Test Ulnar-ADM](image2)

**Figure 2** Prolonged exercise test measuring the right ulnar-ADM CMAP
CASE DISCUSSION

After more than 2 years of follow up, this patient’s symptoms remained relatively stable. There was no development of cardiac or pulmonary abnormalities. While mexiletine was offered to the patient, he did not feel he required therapy for his symptoms, as he felt them to be nondisabling.

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Dr. Han is an associate professor in the Department of Physical Medicine and Rehabilitation (PM&R) at the University of California (UC) Davis. He is also the director of the neuromuscular medicine fellowship and co-director of the Muscular Dystrophy Association Neuromuscular Diseases Clinic at UC Davis. He completed his undergraduate studies at Stanford University with honors, and attended UC San Francisco School of Medicine. He completed his internship and PM&R residency at the University of Washington, and subsequently completed a focused clinical and research fellowship (National Institute of Health K12) in neuromuscular disorders. Dr. Han has clinical focus in neuromuscular diseases affecting both adult and pediatric populations, specifically the various muscular dystrophies, as well as electrodiagnosis. His research interests focus on the development of functional outcome measures in patients with neuromuscular disorders and research using electrodiagnosis/electromyography in the animal models of various neuromuscular diseases.

Craig M. McDonald, MD
Professor
Departments of Physical Medicine and Rehabilitation and Pediatrics
University of California Davis School of Medicine
Davis, California

Dr. McDonald is professor of physical medicine and rehabilitation and pediatrics and director of the Neuromuscular Disease Clinics at the University of California Davis Medical Center. He is director of the National Institute on Disability and Rehabilitation - Research's Rehabilitation Research and Training Center in Neuromuscular Diseases at UC Davis. His research interests include clinical endpoints in muscular dystrophy, exercise in neuromuscular disease, energy expenditure, quantitative assessment of physical activity, and quality-of-life assessment.

Steven Vernino MD, PhD
Associate Professor of Neurology
Neurology Residency Program Director
University of Texas Southwestern Medical Center
Dallas, Texas

Dr. Vernino is associate professor of neurology and integrative biology and director of the neurology residency training program at the University of Texas Southwestern Medical Center in Dallas. He received his medical degree and PhD in neuroscience from Baylor College of Medicine in Houston and then completed residency and fellowship training in neurology and neuroimmunology at Mayo Clinic, Rochester. He is the 1998 winner of the American Academy of Neurology Founders Award for Clinical Neurology Research, and an elected fellow member of both the American Academy of Neurology and American Neurological Association. Dr. Vernino has a special interest in autoimmune and paraneoplastic disorders of the nervous system. His recent research efforts have focused on the characterization of autoimmune autonomic ganglionopathy, an antibody-mediated disorder that causes severe peripheral autonomic failure. His work has led to novel diagnostic and therapeutic techniques for this disorder.

Gil I. Wolfe, MD
Professor
Department of Neurology
University of Texas Southwestern Medical School
Dallas, Texas

Dr. Wolfe is a professor of neurology at University of Texas (UT) Southwestern Medical School in Dallas, Texas. In September 2004, he was named to the Dr. Bob and Jean Smith Foundation Distinguished Chair in Neuromuscular Disease Research. He serves as co-director of the Muscular Dystrophy Association Clinics and director of the Peripheral Neuropathy Clinic at UT Southwestern. He is also medical director and acting vice-chair for the department. Dr. Wolfe completed his undergraduate studies at Princeton University and attended medical school at UT Southwestern. He completed an internal medicine internship and trained as a neurology resident and neuromuscular/electromyography fellow at the University of Pennsylvania Medical Center in Philadelphia. His main research interests include idiopathic and immune-mediated peripheral neuropathies and myasthenia gravis. Dr. Wolfe has received the Trehpine Cranium Award for excellence in residency teaching on several occasions. He also serves on the medical advisory boards for the Myasthenia Gravis Foundation of America, Charcot-Marie-Tooth Association, and Neuropathy Association, and has been elected to Fellow of the American Academy of Neurology and a member in the American Neurological Association. He is certified by the American Board of Psychiatry and Neurology in neurology, neuromuscular medicine, and in clinical neurophysiology.
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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. After attending both sessions, 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 hereditary peripheral neuropathy, paraneoplastic disorders, and DMD and rehabilitation issues at different ages, from childhood to teenage/young adult years.

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

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

CME CREDIT
The AANEM designates this activity for a maximum of 3.25 AMA PRA Category 1 Credit(s). If purchased, the AANEM designates this activity for 2 AMA PRA Category 1 Credit(s). This educational event is approved as an Accredited Group Learning Activity under Section 1 of the Framework of Continuing Professional Development (CPD) options for the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada. Each physician should claim only those hours of credit he or she actually spent in the educational activity. CME for this course is available 10/09 - 10/12.
### 2008-2009 AANEM COURSE COMMITTEE

<table>
<thead>
<tr>
<th>Name</th>
<th>City</th>
<th>State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shawn J. Bird, MD</td>
<td>Philadelphia</td>
<td>Pennsylvania</td>
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<td>Gary L. Branch, DO</td>
<td>Dewitt</td>
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<td>Mazen M. Dimachkie, MD</td>
<td>Kansas City</td>
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<td>Augusta</td>
<td>Georgia</td>
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<td>David Bryan Shuster, MD</td>
<td>Dayton</td>
<td>Ohio</td>
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<tr>
<td>Benjamin S. Warfel, II, MD</td>
<td>Lancaster</td>
<td>Pennsylvania</td>
</tr>
</tbody>
</table>

### 2008-2009 AANEM PRESIDENT

- Michael T. Andary, MD, MS  
  East Lansing, Michigan
Hereditary Peripheral Neuropathy, Variability of Presentations

Gil I. Wolfe, MD
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CASE 1 DESCRIPTION

History

A 3-year-old boy presented with a history of weakness and falling. Examination revealed diffuse weakness that was distal more than proximal, a positive Gower sign, and absent deep tendon reflexes. The child could walk, but had a stumbling pattern.

Past medical and medication histories were unremarkable. Family history was notable, as the biological father was reported to have Friedreich ataxia. The child was adopted at 3 weeks of age.

Initial laboratory studies

Nerve conduction studies (NCSs) were performed and revealed a sensorimotor polynyneuropathy with severe motor conduction slowing in the 6-7 ms range. Routine laboratory studies were unrevealing. A left sural nerve and left quadriceps muscle biopsy were performed at that time. The biopsy material confirmed a neurogenic process with evidence for a demyelinating neuropathy.

Patient course

During the patient's childhood and teenage years, there was progression of motor and sensory deficits. He also developed kyphoscoliosis, and at age 15, underwent a spinal fusion that was complicated by infection that required the removal of instrumentation, as well as several hospitalizations. Prior to the spinal surgery, he could walk for short distances. However, his weakness worsened as a result of the surgical complications. Subsequently, he became wheelchair dependent by age 16. Examination at this time showed severe atrophy in all limbs that was primarily distal to the elbows and knees, flail feet, claw deformities of his hands, absent tendon reflexes and sensory loss distal to the elbows and knees, although position sense remained intact. He could stand in his ankle foot orthotics (AFOs) with moderate support, but could not walk.

Between age 18 and 21, following transfer to the adult neuromuscular (NM) clinic, his examination showed normal cranial nerve function except for mildly reduced facial strength (Medical Research Council [MRC] grade 4). Tongue strength was normal without atrophy or fasciculation. Neck flexion was 4+, neck extension 5, proximal arm muscles 2+ to 3, except for 4 on elbow extension, and 0 to trace in more distal groups. He had claw deformities of the hands. The patient had no movement in his lower limbs with the exception of a 1 to 2 strength in hip flexors/extensors. He remained areflexic and had an absence of vibratory sense at his toes and knees, and reduction at his fingers, wrist, and elbows. Pinprick was decreased distal to the ankles. He remained wheelchair bound and had problems with pedal edema. He could assist with transfers to a shower chair or commode and perform activities of daily life (ADLs) with minimal assistance. The patient was enrolled in a high school equivalence degree program.

Current laboratory studies

Peripheral myelin protein 22 (PMP22) molecular analysis that included testing for point mutations was unremarkable. Cardiac evaluation including Holter and echocardiogram were normal. Lower limb doppler studies were negative. Taking 25 mg of hydrochlorothiazide daily proved helpful for the foot swelling and was well tolerated.
DIFFERENTIAL DIAGNOSIS

Hereditary neuropathies

Hereditary neuropathies are common and are found in 1 of every 2500 individuals worldwide. They typically follow a symmetrical pattern with predominantly distal motor and sensory deficits. Most of these neuropathies fall under the eponym of Charcot-Marie-Tooth (CMT) disease, named to recognize the three investigators who over a century ago first described a dominantly inherited progressive length dependent neuropathy affecting myelinated sensory and motor fibers. Over time, severely affected recessive pedigrees and X-linked forms of hereditary neuropathy were described.

In a second nomenclature introduced by Dyck and colleagues at the Mayo Clinic, Rochester, these disorders are known as hereditary motor and sensory neuropathies (HMSN). These investigators demonstrated that most pedigrees had HMSN1 (or CMT1) characterized by slow conduction velocities (CVs) <40 m/s in the upper limbs and segmental demyelination and remyelination on histology. Harding and Thomas proposed that motor CVs <38 m/s in the forearm could be used to distinguish CMT1 from CMT2, the two most common forms of hereditary neuropathy. Although this has proven useful in planning initial molecular testing in patients with hereditary neuropathy, exceptions to this rule have certainly been reported as genetic testing has become more widespread. Furthermore, dominantly inherited forms of CMT with intermediate CVs have been described (Table 1).

There are many forms of hereditary neuropathy. They are usually classified by the pattern of inheritance, the classes of nerve fibers affected, and whether the nerve injury is predominantly axonal or demyelinating (Table 1). Congenital hypomyelinating neuropathy refers to severe neuropathies presenting in infancy and Dejerine-Sottas to those with onset before age 3 years. Genetic heterogeneity in these two groups of disorders has prompted the proposal that the two terms be removed from genetic classifications. In the hereditary sensory and autonomic neuropathies (HSN or HSAN), sensory (and variably autonomic) neurons or axons are affected, whereas motor neurons or axons are completely or relatively spared; the converse holds for the hereditary motor neuropathies (HMN). Work over the last three decades has demonstrated that mutations in genes expressed by myelinating Schwann cells are largely responsible for demyelinating varieties, whereas mutations in genes expressed by neurons produce the axonal forms of CMT.

The autosomal dominant forms of CMT represent the most commonly inherited NM disorders and are divided into demyelinating (CMT type 1) and axonal (CMT type 2) neuropathies as determined by NCS. Approximately 1 in every 2500 individuals has autosomal dominant CMT. Symptoms usually begin in the second decade, but there is a large range of phenotypic variability even among members of the same family. At times, relatives may be unaware they have attributed mild symptoms to another process. It is estimated that 15% of patients with CMT type 2 present after the age of 50 years. Therefore, a late age of onset does not exclude the possibility of a hereditary neuropathy. A neuropathy that has progressed slowly over several decades should also raise suspicion of a hereditary process. If the family history is unclear, relatives should be examined and tested with NCSs to determine if a familial neuropathy is present.

Table 1. Classification of hereditary sensory, motor, and autonomic neuropathies with associated chromosome loci and genes if known

<table>
<thead>
<tr>
<th>CMT1 (dominant/X-linked demyelinating)</th>
<th>Disease (OMIM)</th>
<th>Locus</th>
<th>Gene</th>
<th>Distinctive Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNPP (162500)</td>
<td>17p11</td>
<td>PMP22</td>
<td>Deletion of PMP22 region, asymmetry due to focal lesions, tomaculae on biopsy</td>
<td></td>
</tr>
<tr>
<td>CMT1A (118220)</td>
<td>17p11</td>
<td>PMP22</td>
<td>Duplication of PMP22 region, most common form of CMT1, onset usually in first two decades, deafness and vocal cord involvement in some, mean CVs in 17-20 ms range, onion bulbs on biopsy</td>
<td></td>
</tr>
<tr>
<td>CMT1B (118200)</td>
<td>1q22-23</td>
<td>MPZ</td>
<td>Mostly point mutations, early onset seen and may cause severe disability, marked CV slowing typical, onion bulbs on biopsy</td>
<td></td>
</tr>
<tr>
<td>CMT1C (601098)</td>
<td>16p13</td>
<td>SIM- PLE</td>
<td>Onset usually second decade, CVs in 16-25 ms range, onion bulbs on biopsy</td>
<td></td>
</tr>
<tr>
<td>CMT1D (60787)</td>
<td>10q21</td>
<td>EGR2</td>
<td>Onset usually second decade, scoliosis, CVs &lt;10 ms, onion bulbs on biopsy</td>
<td></td>
</tr>
<tr>
<td>CMTX Type 1 (302800)</td>
<td>Xq13.1</td>
<td>GJB1/ CX32</td>
<td>Semidominant, males more severely affected, intermediate CVs, hearing loss, episodic weakness, transient encephalopathy at high altitudes</td>
<td></td>
</tr>
<tr>
<td>CMTX Type 2 (302801)</td>
<td>Xp22.2</td>
<td></td>
<td>Recessive, onset first decade, mental retardation</td>
<td></td>
</tr>
<tr>
<td>CMTX Type 3 (302802)</td>
<td>Xp26.3-27.1</td>
<td></td>
<td>Recessive, onset first to second decade, pain and paresthesias</td>
<td></td>
</tr>
<tr>
<td>CMTX Type 4 (310490)</td>
<td>Xq24-26.1</td>
<td></td>
<td>Recessive, onset by 5 years with deafness, mental retardation, CVs 33 ms to normal</td>
<td></td>
</tr>
<tr>
<td>CMTX Type 5 (300563)</td>
<td>Xq22.3</td>
<td>PRPS1</td>
<td>Recessive, onset first decade, hearing loss, optic atrophy, CVs mildly slowed to normal</td>
<td></td>
</tr>
</tbody>
</table>
### Dominant intermediate CMT

<table>
<thead>
<tr>
<th>Disease (OMIM)</th>
<th>Locus</th>
<th>Gene</th>
<th>Distinctive Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>DI-CMTA (606483)</td>
<td>10q24.1-25</td>
<td></td>
<td>Onset in first to second decade, distal weakness and mild sensory loss, CVs 25-45 ms</td>
</tr>
<tr>
<td>DI-CMTB (696482)</td>
<td>19p12-13.2</td>
<td>DNMT2</td>
<td>Allelic with centronuclear myopathy and CMT2 syndromes, distal motor and sensory involvement, some with tremor, cataracts and ophthalmoparesis, CVs 20-50 ms, rare onion bulbs on biopsy</td>
</tr>
<tr>
<td>DI-CMTC (608323)</td>
<td>1p35</td>
<td>YARS</td>
<td>Onset usually in first to second decade, distal motor and mild sensory involvement, CVs 30-50 ms</td>
</tr>
</tbody>
</table>

### CMT2 (dominant axonal/neuronal)

<table>
<thead>
<tr>
<th>Disease (OMIM)</th>
<th>Locus</th>
<th>Gene</th>
<th>Distinctive Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT2A1 (118210)</td>
<td>1p36.2</td>
<td>KIF1B</td>
<td>Similar to CMT2A2</td>
</tr>
<tr>
<td>CMT2A2 (699260)</td>
<td>1p36.2</td>
<td>MFN2</td>
<td>Most common form of CMT2, severe forms with optic atrophy, myelopathy</td>
</tr>
<tr>
<td>CMT2B (600882)</td>
<td>3q21</td>
<td>RAB7</td>
<td>Severe sensory loss, acromutlulation, foot ulcers</td>
</tr>
<tr>
<td>CMT2C (606071)</td>
<td>12q23-24</td>
<td></td>
<td>Diaphragm and vocal cord weakness, minimal sensory involvement</td>
</tr>
<tr>
<td>CMT2D (601472)</td>
<td>7p15</td>
<td>GARS</td>
<td>Allelic with HMSN V, onset with hand weakness, variable sensory involvement</td>
</tr>
<tr>
<td>CMT2E (162280)</td>
<td>8p21</td>
<td>NEFL</td>
<td>Also described as CMT1F, episodic ataxia, hearing loss, postural tremor, giant axons on biopsy</td>
</tr>
<tr>
<td>CMT2F (606595)</td>
<td>7q11.23</td>
<td>HSPB1</td>
<td>Weakness can be severe, variable sensory involvement, fasciculations in some</td>
</tr>
<tr>
<td>CMT2G (608591)</td>
<td>12q12-q13.3</td>
<td></td>
<td>Widely variable age of onset, slowly progressive distal weakness</td>
</tr>
<tr>
<td>CMT2 (604484)</td>
<td>3q13.1</td>
<td></td>
<td>Cramps prominent, proximal-distal weakness, 40% with diabetes, spinal cord involvement, elevated CK</td>
</tr>
</tbody>
</table>

### Severe (dominant or recessive) demyelinating neuropathies

<table>
<thead>
<tr>
<th>Disease (OMIM)</th>
<th>Locus</th>
<th>Gene</th>
<th>Distinctive Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dejerine-Sottas neuropathy/HMSN-III/CMT3 (145900)</td>
<td>17p11 1p22 Xq13.1 10q21 19q13.1 8p21</td>
<td>PMP22 MPZ GJB1 EGR2 PRX NEFL</td>
<td>Onset &lt;3 years, delayed motor milestone, ambulation aids or wheelchairs usually needed over time, kyphoscoliosis, prominent foot deformities, nerve enlargement, very slow CVs (often in single digits)</td>
</tr>
<tr>
<td>Congenital hypomyelinating neuropathy (605253)</td>
<td>10q21 17p11 1p22</td>
<td>EGR2 PMP22 MPZ</td>
<td>Arthrogryposis, early death in severe cases, diffuse distal&gt;proximal weakness, very slow CVs (&lt;10 ms) thin or absent myelin on biopsy</td>
</tr>
</tbody>
</table>

### Recessive demyelinating neuropathy (CMT4)

<table>
<thead>
<tr>
<th>Disease (OMIM)</th>
<th>Locus</th>
<th>Gene</th>
<th>Distinctive Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT4A (214400)</td>
<td>8q13-q21.1</td>
<td>GDAP1</td>
<td>Onset &lt;2 years, rapidly progressive motor deficits, CVs 25-35 ms, hypomyelination, and onion bulbs on biopsy</td>
</tr>
<tr>
<td>CMT4B-1 (601382)</td>
<td>11q22</td>
<td>MTMR2</td>
<td>Onset &lt;4 years, typically wheelchair bound as adults, CVs&lt;20 ms, prominent lips, redundant myelin loops on biopsy</td>
</tr>
<tr>
<td>CMT4B-2 (604563)</td>
<td>11p15</td>
<td>MTMR13 SBF2</td>
<td>Allelic with HMSN with focally folded myelin sheaths, onset 1st to 2nd decade, CVs 15-30 ms, redundant myelin loops, and onion bulbs on biopsy</td>
</tr>
</tbody>
</table>
CMT4C (601596) 5q32 SH3TC2 Fairly frequent form of AR CMT, onset through adolescence, scoliosis, cranial nerve involvement with deafness, nystagmus, unresponsive pupils, tongue atrophy

CMT4D-Lom (601455) 8q24.3 NDRG1 Onset first decade, severe disability by mid-adulthood, scoliosis, deafness, CVs<20 ms, Schwann cell inclusions, endoneurial collagenization on biopsy

CMT4E 10q21 EGR2 Redundant myelin folds

CMT4F (605260) 19q13 PRX Onset 1st decade, ataxic gait, severe sensory loss, mild kyphoscoliosis, slow progression, redundant myelin folds

CMT 4G/ HMSN-R (605285) 10q23.2 FGD4 Age <2 years, scoliosis, CVs <15 ms

CMT4H (609311) 12p11.21- q13.11 FGD4 Allelic with CMT4A, can also be AD, onset <2 years, vocal cord paralysis and hoarseness, wheelchair bound by second decade

### Hereditary Sensory and Autonomic Neuropathies (HSAN)

<table>
<thead>
<tr>
<th>Disease (OMIM)</th>
<th>Locus</th>
<th>Gene</th>
<th>Distinctive Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSAN1/HSN1 (162400)</td>
<td>9q22.1-22.3</td>
<td>SPTLC1</td>
<td>AD, onset second decade or later, Charcot joints, chronic ulcers, acromutilation weakness possible late in course, variable deafness, less prominent autonomic involvement than other forms</td>
</tr>
<tr>
<td>HSAN1B (608088)</td>
<td>3p22-24</td>
<td></td>
<td>AD, onset second to fifth decades, begins with cough and gastroesophageal reflux</td>
</tr>
<tr>
<td>HSAN2 (201300)</td>
<td>12p13.33</td>
<td>HSN2/ WNK1</td>
<td>AR, reduced distal sweating, episodic compensatory hyperhidrosis, tonic pupils, skin ulcers, acromutilation</td>
</tr>
<tr>
<td>HSAN3 (223900)</td>
<td>9q31</td>
<td>IKB- KAP</td>
<td>AR, congenital onset, absent fuguiform tongue papillae, pain insensitive, emotional crises, postural hypotension, gastrointestinal dysmotility, scoliosis, restrictive lung disease, central apnea, often fatal by mid adulthood</td>
</tr>
<tr>
<td>HSAN4 (256800)</td>
<td>1q21-q22</td>
<td>NTRKA</td>
<td>AR, congenital onset, anhidrosis, insensitivity to pain, mental retardation, self mutilation, early death observed</td>
</tr>
<tr>
<td>HSAN5 (162030)</td>
<td>1p13.1</td>
<td>NGFB</td>
<td>AR, congenital onset, acromutilation, no anhidrosis</td>
</tr>
<tr>
<td>Familial/primary erythromelalgia (133020)</td>
<td>2q31</td>
<td>SCN9A</td>
<td>AD, intermittent distal burning pain triggered by warmth/exercise/standing associated with red congestion, vasodilatation of skin</td>
</tr>
<tr>
<td>cold-induced sweating (272430)</td>
<td>19p12</td>
<td>CRLF1</td>
<td>AR, onset first to second decade, small fiber sensory loss, depressed nasal bridge, high-arched palate, nasal voice, clindac- tely, elbow contractures, kyphoscoliosis, reduced interest in feeding</td>
</tr>
<tr>
<td>HSN with cough and gastroesophageal reflux (608088)</td>
<td>3p22-p24</td>
<td></td>
<td>Allelic with HSAN1B (see above)</td>
</tr>
</tbody>
</table>

### Recessive Axonal Neuropathy

<table>
<thead>
<tr>
<th>Disease (OMIM)</th>
<th>Locus</th>
<th>Gene</th>
<th>Distinctive Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR-CMT2A (605588)</td>
<td>1q21.2</td>
<td>LMNA</td>
<td>Allelic with limb girdle muscular dystrophy 1B, AD Emery-Dreifuss muscular dystrophy, AD dilated cardiomyopathy, familial partial lipodystrophy; onset 2nd decade, severe phenotype, scapular weakness, kyphoscoliosis</td>
</tr>
<tr>
<td>AR-CMT2B (605589)</td>
<td>19q13.3</td>
<td>MED25</td>
<td>Adult onset, distal cramps and paresthesias</td>
</tr>
<tr>
<td>CMT2K (607831)</td>
<td>8q13-q21.1</td>
<td>GDAP1</td>
<td>Allelic with CMT4A, can also be AD, onset &lt;2 years, vocal cord paralysis and hoarseness, wheelchair bound by second decade</td>
</tr>
</tbody>
</table>
### Hereditary Motor Neuropathies (HMN)

<table>
<thead>
<tr>
<th>Disease (OMIM)</th>
<th>Locus</th>
<th>Gene</th>
<th>Distinctive Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMN1 (182960)</td>
<td>7q34</td>
<td>AD, onset up to fifth decade, slow progression</td>
<td></td>
</tr>
<tr>
<td>HMN2A (158590)</td>
<td>12q24</td>
<td>HSPB8</td>
<td>AD, allelic with CMT2L, onset second to fourth decade, progression over 5 years to complete distal paralysis</td>
</tr>
<tr>
<td>HMN2B (608634)</td>
<td>7q11.23</td>
<td>HSPB1</td>
<td>AD or AR, allelic with CMT2F</td>
</tr>
<tr>
<td>HMN 3&amp;4 (607088)</td>
<td>11q13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMN5A (600794)</td>
<td>7p15</td>
<td>GARS</td>
<td>AD, allelic with CMT2D, onset in second decade, upper limbs involved first, rare pyramidal signs</td>
</tr>
<tr>
<td>HMN5B (600794)</td>
<td>11q13</td>
<td>BSCL2</td>
<td>AD, common form in Europe, onset up to fourth decade, early hand involvement, pyramidal signs, mild proprioceptive loss, slow progression</td>
</tr>
<tr>
<td>HMN6/ SMARD1 (604320)</td>
<td>11q13.2-13.4</td>
<td>IGHMBP2</td>
<td>AR, onset by 2 years, diaphragm paralysis, early death from respiratory failure</td>
</tr>
<tr>
<td>HMN7A (158580)</td>
<td>2q14</td>
<td></td>
<td>AD, onset by second decade, vocal cord and respiratory involvement, hand onset, some with hearing loss, slow progression</td>
</tr>
<tr>
<td>HMN7B (607641)</td>
<td>2p13</td>
<td>DCTN1</td>
<td>AD, onset in early adulthood, vocal cord and respiratory involvement, facial weakness</td>
</tr>
<tr>
<td>HMN X-linked (300489) SMAX3</td>
<td>Xq13.1-q21</td>
<td>Recessive, onset through fifth decade, some weaker in cold</td>
<td></td>
</tr>
<tr>
<td>HMN/ALS4 (602433)</td>
<td>9q34</td>
<td>SETX</td>
<td>AD, juvenile onset, upper motor neuron signs, slowly progressive, axonal swelling on biopsy</td>
</tr>
<tr>
<td>congenital distal SMA (600175)</td>
<td>12q23-q24</td>
<td>AD, similar to HMN1, contractures, nonprogressive</td>
<td></td>
</tr>
</tbody>
</table>

Key: AD-autosomal dominant; AR-autosomal recessive; BSCL2-Berardinelli-Seip congenital lipodystrophy 2 (seipin); CK-creatine kinase; CMT-Charcot-Marie-Tooth disease; CRLF1-cytokine receptor-like factor 1; CV-conduction velocity; DCTN1-dynactin; DNM2-dynamin 2; EGR2-early growth response 2; FIG4-factor-induced gene 4; GARS-glycyl-tRNA synthetase; GDAP1-ganglioside-induced differentiation-associated protein 1; GJB1-connexin 32; HMN-hereditary motor neuropathy; HNPP-hereditary neuropathy with liability to pressure palsies; HSAN-hereditary sensory and autonomic neuropathy; HSN2-hereditary sensory neuropathy 2; HSPB1-heat shock protein 1; HSPB8-heat shock protein 8; IGHHMBP2-immunoglobulin mu binding protein 2; IKBKG-inhibitor of κ light polypeptide gene enhancer in B cells, kinase complex-associated protein; KIF1B-kinesin family member 1B; LMNA-lamin A/C; MED25-mediator of RNA polymerase II transcription, subunit 25 homolog; MFN2-mitofusin 2; MPZ-myelin P0 protein; MTMR2-myotubular related protein 2; MTMR13-myotubular related protein 13; NDRG1-N-myc downstream-regulated gene; NELF-neurolfilament light chain; NGRB-nerve growth factor receptor; OMIM-online Mendelian inheritance in man; PMP22-peripheral myelin protein 22; PRPS1-Phosphoribosylpyrophosphate synthetase 1; PRX-periaxin; RAB7-RAS-related GTP binding protein 7; SCN9A-sodium channel 9A; SEPT9-septin 9; SETX-septins; SH3TC2- SET binding factor 2; SH3TC2- SH3 domain and tetratricopeptide repeat domain 2; SMARD1-six integral membrane protein of lysosome/late endosome; SMA-spinal muscular atrophy; SPTLC1-serine palmitoyltransferase long-chain base subunit 1; YARS-tyrosyl-tRNA synthetase.

Molecular testing for several forms of hereditary neuropathy, particularly the most common ones, is commercially available. These include: PMP22, MPZ, GJB1 (CX32), EGR2, SIMPLE (LITAF), GARS, RAB7, NEFL, HSPB1, PRX, LMNA, GDAP1, SH3TC2, and FIG4. (see table key above). Clinicians should be wary, however, of the value of the larger and expensive panels of tests offered through these services as they often are not phenotype specific. Testing for other genes may be found at http://www.genetests.org where information on the limitations of testing and qualifications of laboratories is also available. An important point is that the yield for molecular testing is much higher for demyelinating than axonal forms of CMT. To avoid unnecessary testing and potentially misleading results, it is best to focus on molecular testing after defining the mode of transmission, associated systemic features, and NCS results.

Other types of hereditary neuropathy are less common (Table 1). HSAN mainly affect small myelinated and unmyelinated sensory fibers, resulting in marked loss of pain and thermal sensation. There is variable loss of other sensory modalities. Autonomic dysfunction may also be present. Pressure sores, foot ulcers, and Charcot joints result from repeated trauma to insensitive distal limbs. Familial dysautonomia, or Riley-Day syndrome, is included in this family of hereditary neuropathies.

### EVALUATION

Because as many as 30% of undiagnosed neuropathies may have a hereditary basis, it is important to search for clues in the history and examination that suggest the presence of a hereditary disorder before embarking on an expensive evaluation. The presence of high-arched feet (pes cavus), clawed toes and/or hands, scoliosis, enlarged nerve trunks, Charcot joints, and onset in the first two to three decades of life are strongly suggestive of hereditary neuropathy. The patient described shares several of these features including very early onset, clawed hands, and kyphoscoliosis.
The NCS data in this case is consistent with a severe demyelinating process, allowing for a more focused approach to available molecular testing. The biological father had been diagnosed with Friedreich ataxia on clinical grounds by history, but it would be reasonable to assume he and his son have the same underlying process and that the hereditary ataxia diagnosis was incorrect. An autosomal dominant pattern is implied, as there is male to male transmission if one assumes the father and son share the same disease process.

The primary considerations in this patient, given the sensory and motor involvement, would be a severe form of CMT type 1 (1B and 1D deserve particular attention), and a dominant form of CMT type 3 or Dejerine-Sottas disease. An HMN or HSAN would be less likely based on the presentation.

Diagnostic Study

After PMP22 testing returned normal, MPZ molecular analysis was reviewed and revealed a heterozygous Ser34Cys substitution. This MPZ mutation is one of several that is linked with severe CMT1 phenotypes and Dejerine-Sottas neuropathy.

MANAGEMENT

There is no specific therapy available for hereditary neuropathies at this time. AFOs have proven to be very helpful in patients who develop significant foot drop. The vast majority of patients with CMT remain ambulatory to some extent throughout their lives, although the patient described fell into the 10% subpopulation that becomes wheelchair dependent. Management will be discussed further in regards to physical medicine approaches to hereditary neuropathies.

REHABILITATION MANAGEMENT

This is an unusual case with very early presentation of symptomatology. While there are no specific curative therapies currently available for the hereditary neuropathies, there are a number of treatment strategies that can help improve quality of life.

Neurodevelopmental Physical and Occupational Therapy Program

Given the fact that the presentation occurred in early childhood as opposed to a more typical later onset in late adolescence or early adulthood, there will be neurodevelopmental problems that will need to be addressed. Neurodevelopmental therapy (NDT) is a problem solving approach to the examination and treatment of the impairments and functional limitations of individuals with NM disorders such as CMT or muscular dystrophy.

Clearly, this child has dysfunction in gait and posture. This will create movement that leads to limitations in functional activities. An NDT program will focus on the analysis and treatment of sensorimotor impairments and functional limitations. In this case, the NDT program should include both physical therapists and occupational therapists (OT). There is an emerging body of evidence indicating that some forms of CMT do involve central demyelination which could potentially produce some learning problems. If this is a concern, brain imaging and consultation with a speech and language pathologist (SLP) would also be indicated.

A thorough examination and evaluation is the basis for treatment. The examination begins with the identification of an individual's abilities and limitations. This child has significant muscle weakness that is more predominant in the distal musculature. From a rehabilitation standpoint, the initial examination should focus on identifying functional limitations. Evaluation analyzes and prioritizes the effectiveness of posture and movement leading to the establishment of treatment goals and the development of treatment strategies commensurate with the child's current needs, while at the same time, aiming for the long-term outcome of achieving the best possible function across the lifespan.

When dealing with a child with severe NM dysfunction, it is critical that the clinician understands how the disease will change across the lifespan, which will provide a critical framework for long term treatment planning. In addition, the clinician must anticipate the progression of atypical postures and movements and understand how they will change as the child develops and grows.

The therapists should develop exercise strategies that will facilitate postural control and movement synergies that improve locomotion. The therapist should also inhibit or constrain those motor patterns that are abnormal and may lead to secondary deformities and produce even further disability. As the child grows, these strategies will minimize secondary impairments that can create additional functional limitations or disabilities.

Bracing/Orthotics

This child, like most patients with CMT, will require some form of bracing or orthotics for their lower extremities (LEs). A variety of products are available, and selection is of utmost importance for a successful outcome. The traditional double upright metal AFO attached to the shoe is infrequently prescribed, compared to the less obtrusive plastic polypropylene orthosis. Metal bracing is appropriate for patients with fluctuating edema. Traditionally, the double upright metal AFO was preferred in severe cases of sensory neuropathy due to a risk of skin breakdown from snug fitting plastic orthosis, but certain neuropathy patients that are nearly insensate do well in plastic orthoses as long as they adhere to a strict wearing schedule, maintain good skin care, and have frequent reevaluations by the orthotist.

As a general rule, patients with CMT, including children, are not well served by prefabricated orthotics. A trial with an off the shelf device may be appropriate during physical or occupational therapy. However, for patients requiring an orthosis for ambulation, utilizing a device that fits well provides more comfort and better wearing compliance, as well as helping to avoid risk for skin breakdown.
CMT usually causes significant proprioceptive loss, along with weakness of the primary ankle invertors (tibialis anterior and posterior muscles) and evertors (peroneus longus and brevis muscles). Instability of ankle inversion and eversion may occur before deficits of dorsiflexion and plantar flexion become apparent. In this situation, there is obvious ankle weakness, and gait observation shows significant deficits. Orthotic management in these cases focuses on using the least restricting orthosis while providing support for the subtalar joint. Because there is frequently coexisting involvement of intrinsic foot muscles with forefoot proprioceptive loss, ankle bracing is often combined with a foot orthosis or shoe modification. Failure to brace in this situation may produce substantial damage to the ankle joint, producing a so called “Charcot arthropathy”. Bracing is particularly important in a young child, as there will be a lifetime of ankle stress.

A full thermoplastic or metal double upright AFO provides maximal mediolateral support for the ankle. These braces are also quite durable, which is a consideration with children. In addition to managing dorsiflexion weakness and mediolateral instability, limiting dorsiflexion in terminal stance assists with plantar flexion weakness that should normalize heel rise and improve velocity and step length. A stiff, nonarticulated plastic AFO accomplishes these goals. Anterior trim lines, thicker gauge plastic, or carbon fiber reinforcements supply the additional stiffness. It is worth noting that most CMT patients will require a short course of physical therapy to help them use these braces effectively. This can be incorporated into the described child’s neurodevelopmental program. Because the child will be growing, frequent AFO changes will be necessary and the fit should be monitored closely. Often young children will need new AFOs every 6 to 9 months due to growth.

**Equipment**

There are a number of additional useful equipment items that can substantially help improve a patient’s quality of life. These include hand held showers, bath tub benches, grab bars, raised toilet seat, hospital bed, commode chair, and ADL aids (sock aid, grabbers, etc.). Wheeled walkers or quad (four point) canes may also help, depending on the pattern of weakness. In more severe cases of CMT, a wheelchair may be necessary. Wheelchairs should be properly fitted (generally by an OT) and have adequate lumbar support and good cushioning to avoid pressure ulcers. If the upper extremities (UEs) are very weak, a power wheelchair will be necessary to maintain independent mobility and thus, markedly improve the patient’s quality of life. Given the very early presentation in this case, it is highly likely this patient will encounter the need for durable medical equipment as he enters adulthood.

**Vocational Issues**

As this patient matures, vocational and societal integration issues will become important. It would appear that pain, depression, and other indicators of altered personality profiles can substantially impact social integration and employment rates, and might be as important as physical abilities in this patient population. A large percentage of these patients exhibited elevated scores for bodily pain and depression on standardized testing, including the Short-Form Health Survey 36, Brief Pain Inventory, and the Minnesota Multiphasic Personality Inventory test. Thus, these factors should be assessed and treated.

The vast majority of patients with CMT have intellectual levels within the normal range. However, employment rates for this population are substantially lower than for the able bodied. Indicators of emotional pathology appeared to be associated with unemployment, whereas loss of ambulation and arm function was not. Higher levels of education correlated with higher employment rates and improved self esteem in this group.

**OTHER ISSUES IN CMT**

As this patient ages into adulthood, a number of other medical and rehabilitation issues may occur. These will be briefly discussed.

**Weakness and Fatigue**

Skeletal muscle weakness and fatigue are the underlying causes of the majority of clinical problems in CMT. There have been several well-controlled, class II studies that examine the effect of exercise as a means to gain strength in CMT and other neuromuscular disorders (NMDs). In slowly progressive NMDs, including CMT, a 12-week, moderate-resistance (30% of maximum isometric force) exercise program resulted in strength gains ranging from 4-20% without any notable deleterious effects. However, in the same population, a 12-week, high-resistance (training at the maximum weight a subject could lift 12 times) exercise program showed no further benefit as compared to the moderate resistance program, and there was evidence of overwork weakness in some of the subjects. The risk of muscle damage and dysfunction secondary to exhaustive exercise may be significant, and neuropathy patients should be advised not to over exercise. Overwork weakness involves feeling weaker rather than stronger within 30 minutes after exercise or excessive muscle soreness 24 to 48 hours after exercise. Other warning signs include: severe muscle cramping, heaviness in the extremities, and prolonged shortness of breath.

In a comparative study, CMT patients appeared to benefit significantly from a strengthening program, whereas patients with myotonic muscular dystrophy in the same study showed no beneficial or detrimental effects. Exercise in CMT can induce muscle cramps, impairing fine motor movements. Warm-up and cool-down sessions are helpful. These include slow, static muscle stretching (30 seconds sustained), which also helps maintain flexibility. Proximal muscle weakness is also present in CMT and can be demonstrated through quantitative strength testing. Patients with CMT are more prone to entrapment neuropathies which have been reported with heavy forearm exercise. The neuropathy is progressive, although strength decline does not necessarily parallel decline in conduction velocity and other electrodiagnostic (EDX) parameters.
Clinical management should include early intervention with gentle, low-impact aerobic exercise like walking, swimming, and stationary bicycling. These activities will improve cardiovascular performance, increase muscle efficiency, and may help fight fatigue. Fatigue in peripheral neuropathy is multifactorial and includes impaired muscular activation, generalized deconditioning, and diminished cardiopulmonary performance due to immobility. Aerobic exercise improves not only physical functioning, but is beneficial in fighting depression, maintaining ideal body weight, and improving pain tolerance. Gentle, static stretching should follow exercise as CMT patients are more prone to muscle tendon tightness and joint contractures than an able-bodied person. Thus, if a patient with a CMT develops an injury that requires immobilization (i.e., ankle sprain), joint contractures may occur due to prolonged static positioning of the limb. After the initial immobilization, physical therapy for gentle static stretching and progressive resistive exercise to restore maximal function is essential. Because patients are also at a higher risk for heel cord tightness and frank ankle joint contractures, surgical release and bracing may be necessary to facilitate ambulation.

There are limited modalities to treat fatigue in CMT. Modafinil is used to treat the symptoms of fatigue and excessive daytime sleepiness in narcolepsy. However, fatigue and subsequent excessive daytime sleepiness secondary to fatigue are common symptoms in many neurologic disorders. Prior reports on patients with myotonic muscular dystrophy, multiple sclerosis, Parkinson’s disease, and amyotrophic lateral sclerosis, have shown some beneficial effects from the use of modafinil in treating fatigue. A recent case series of four patients with CMT showed promising relief of fatigue following modafinil treatment.

OTHER POSSIBLE CLINICAL ISSUES

Neuropathic Pain, Breathing, Hearing, Swallowing

A previous study surveying 636 individuals with CMT indicated that 440 (69%) of the respondents had significant pain problems. The nature of the pain is neuropathic and treatment should be approached as such.

There have been numerous case reports of respiratory failure in people with CMT, the etiology of which has remained elusive. EDX and pathologic studies on the phrenic nerve in CMT confirm its involvement in the disease. Phrenic nerve latencies are abnormally prolonged in most CMT1 subjects. However significant pulmonary function test (PFT) abnormalities and clinical symptoms are uncommon and do not appear to correlate with the phrenic nerve latencies. Although phrenic nerve latencies are markedly prolonged in CMT, they are not useful in predicting respiratory dysfunction.

Other less common problems encountered in CMT include sensorineural hearing loss and vocal cord paralysis. A recent study in CMT1A patients with normal peripheral hearing documented subtle auditory processing problems. There may also be specific cranial nerve abnormalities, including papillary changes. These more subtle problems in CMT are postulated to be due to a specific subset of genotypes involving the PMP22, MPZ, and EGR2 genes, among others. These problems should be managed symptomatically. Evaluation by an otolaryngologist, a SLP, or an audiologist may be helpful.

CASE 2 PRESENTATION

History

A 38-year-old woman presented to a NM clinic with the chief complaint of dragging her right foot over the past year.

The patient reported feeling clumsy since childhood, which worsened during her pregnancy 1 year ago. She sprained her right ankle 2 years prior to that. Over the past year, she has noticed difficulty in lifting the toes on her right foot and has also experienced difficulty standing on her toes. She has noted mild weakness in the fingers of her dominant right hand over the past few months. Other than leg and arm weakness, the patient has been healthy without any other reported past medical history.

She denies any neck, back, or leg pain, and denies numbness in the arms or legs.

The patient does not take any medications and has no known drug allergies. She does not smoke or drink alcoholic beverages. She is married and works as an architect.

She has three children, a 7-year-old boy and 4- and 1-year-old girls. The children are able to keep up with their peers without any weakness noted. Her mother has broken her leg twice, but the patient denies that her mother has any weakness. Her father was diagnosed with Alzheimer’s disease at age 75. She has two brothers who do not have any noticeable weakness.

The patient has no complaints regarding her ambulation, although she admits at times she has to “hustle” to keep up with her friends. There are six steps leading to the front door of her condominium building, and the bedrooms are on the second floor.

She has tried physical therapy on a few occasions, but has not found it helpful. The therapists primarily directed her in exercises and provided muscular massage. She does not take any medications.

Physical Examination

Mental status was normal. Cranial nerves were intact, including normal hearing to finger rub and normal speech.

There was no orbicularis oculi/oris or tongue weakness. Motor examination revealed the following MRC scores (0-5 scale, R/L): SA 5/5-, EF 5-/5-, EE 4+/4+, WF/WE all 4+/4+, WF 4+/4+; finger flexors 5-/5-, FDI 4/4, APB 4+/4+, hip flexors 4+/4+, hip abductors/adductors/flexors 5/5, KE/KF 5/5, ADF 3+/4-, APF 4/5-, foot inversion 4/4. Muscle bulk was mildly decreased in the distal LEs and hands. Tone was normal.
Sensory testing revealed mildly decreased light touch/pinprick/ temp (feet 80% of forehead, fingertips 90% of forehead) sensation in all extremities. Joint position sense was decreased in the great toes. Timed vibratory sensation with 128 Hz tuning fork was 8 s at medial ankles.

Reflex testing included brachioradialis 1/4 bilaterally, others absent.

Gait was notable for moderate increase in stance. Slight increased hip flexion was noted in swing phase, especially on right. Unable to heel walk, could toe walk with some difficulty on right. Difficulty with tandem gait. Mild bilateral ankle valgus in stance phase.

**DIFFERENTIAL DIAGNOSIS**

A 39-year-old woman who presents with progressive weakness of multiple limbs raises the following possible diagnoses:

- Multiple sclerosis (MS) commonly presents in females in this age group. However, the lack of significant sensory or visual symptoms make this less likely, and the pattern of weakness is not consistent with upper motor neuron injury commonly seen in MS.

- Chronic inflammatory demyelinating polyneuropathy can present as slowly progressive spreading weakness and numbness.

- Muscular dystrophy or myopathy could possibly present in such a fashion.

- CMT could present with this clinical picture of slowly progressive multifocal weakness without marked sensory complaints. This could either be a demyelinating or axonal form of CMT.

An EDX examination, a sensitive test to differentiate among the diagnostic possibilities, was performed. NCSs revealed prolonged distal latencies and uniform slowing of conduction velocities (16-22 m/s) in the right ulnar/median/tibial/peroneal motor studies. It was necessary to decrease the sweep speed of the NCS recordings to visualize the delayed motor potentials. No conduction block or temporal dispersion was noted. The right radial/median/sural/superficial peroneal sensory studies were notable for absent responses. Needle electromyography was notable for widespread chronic reinnervation.

The lack of conduction block/temporal dispersion and uniform conduction velocity slowing suggested a genetic/hereditary etiology of this demyelinating neuropathy.

There are several explanations for the lack of family history of neuropathy. As reviewed, some forms of demyelinating CMT (CMT4) are autosomal recessive (Table 1). It is possible that the patient’s father is not the genetic parent. Point mutations in PMP22 can occur, although these usually cause a more severe phenotype. The most likely possibility is that the patient has a de novo duplication of PMP22. This can occur from an abnormal crossing over of chromosomes during meiosis.

Genetic testing for demyelinating CMT was performed, which revealed a duplication of PMP22 (CMT1A). About 30% of CMT1A patients have a de novo mutation. This is also seen with other forms of CMT. The frequency of HNPP (PMP22 deletion) patients with de novo mutations has been reported to range from 4.6 to 21%.34,35

The patient was counseled about the genetic etiology of CMT1A. She did not want genetic testing performed on her children at that time. She was encouraged to engage in gentle, low-impact aerobic exercise. She was educated about how to avoid compression of UE nerves while working on a computer and at a desk. Plastic and metal AFOs were discussed; she wanted time to consider the options. A follow-up appointment was scheduled.

**COMMON QUESTIONS AND CONCLUSIONS**

**How is CMT related to pregnancy?**

The interaction of CMT and pregnancy has been examined. A study of 21 patients with CMT1 and their combined total of 45 gestations was notable for 38% of the patients reporting an exacerbation of CMT symptoms during pregnancy, with a temporary increase of weakness in 35% of these exacerbations and permanent increase in weakness in 65%.36 When the patients were divided into groups of those with childhood onset and adult onset CMT1, the childhood onset patients had a 50% risk of pregnancy related exacerbations, while none of the adult onset patients experienced an exacerbation. A study of the Medical Birth Registry of Norway from 1967 to 2002 found that pregnant mothers with CMT had twice the risk of presentation abnormalities (9.3 versus 4.5%) and twice the rate of operative delivery (29.5 versus 15.3%) with more frequent use of forceps (9.3 versus 2.7%).37 However, a comparison of women with/without pregnancy and men with CMT1A found no difference in the CMT Neuropathy Score and Neuropathy Impairment Score between the groups, suggesting that gender and pregnancy do not significantly affect overall severity of neuropathy in CMT1A.38

**What is the news regarding Vitamin C and CMT? Are there any possible side effects if I just take the trial dose on my own?**

Vitamin C in vitro promotes normal myelination in cell cultures. It was found in a CMT1A mouse model to have a marked effect, causing reduction in expression of PMP22 to levels below what is necessary to induce the CMT phenotype.39 Understandably, this paper generated a great deal of interest in human clinical trials on the effect of vitamin C in CMT1A. Most of these trials are still in progress. An early trial of Australian children recently failed to show a significant difference in the primary outcome measure of nerve conduction velocity, although there are difficulties studying CMT in children that could make it difficult to find a significant result.40,41 There is an ongoing trial in the United States that ex-
amines the effect vitamin C has on adults with CMT1A. Patients who investigate vitamin C and CMT on the Internet will find the study dose of 2000 mg bid and may independently take this over the counter supplement. Dosing of vitamin C over 2000 mg per day can cause side effects including gastrointestinal upset, diarrhea, nausea, increased irritation when taken with aspirin, effect on pregnancy, risk of exacerbating existing renal calculi, and worsening of hemochromatosis and G6PD deficiency.

I don't want to wear the visible plastic or metal AFOs. I'm an architect and aesthetics are important to me. Are there any other options?

Many patients, both men and women, are resistant to wearing visible AFO braces. The reasons range from aesthetic issues to reluctance in using assistive equipment that visually identifies them as having impairments. This resistance may not be alleviated by a discussion outlining the benefits or an AFO trial. Alternatives that do not provide the stability of the best AFO materials previously discussed, but which can provide some benefit include graphite AFOs, which do not provide medial/lateral ankle stability but can improve ankle dorsiflexion and improve gait. They are unobtrusive, with only a thin black graphite strut visible between the shoe and pant leg. Several shoe types provide increased ankle stability, including athletic shoe high tops, boots that lace up over the ankle, and cowboy boots. The patient reviewed these options, but still needed time to weigh the options before an AFO decision was made.

REFERENCES

4. Neuromuscular Disease Center Website, Washington University Medical School, http://neuromuscular.wustl.edu/
CASE 1 DESCRIPTION: WEAKNESS AND RASH

History

A 56-year-old woman was in her usual state of health until 18 months prior to being seen for a skin rash on the knuckles of her fingers, and on the front and back of her chest in a scarf-like distribution. A few weeks after the onset of this rash, she developed weakness in her hip and shoulder girdle muscles. She described extreme difficulty getting in and out of a chair, and raising her arms to reach for objects placed on high shelves. She remained ambulatory, but described extreme fatigue and weakness in walking short distances. Serum creatine kinase (CK) was noted to be 5964 IU/L (NL 21-215). Serum aldolase was 68.6 U/L (NL 1.2-7.6 u/L). Antinuclear antibody test (ANA) was >1:640 speckled. Magnetic resonance imaging (MRI) of the muscles showed abnormal signal intensity in thigh and pelvic muscles, bilaterally. A muscle biopsy showed findings of chronic necrotizing myopathy, although neither perifascicular atrophy, nor primary inflammation was noted (Figure 1).

The patient was diagnosed as having dermatomyositis (DM) and was started on a high dose of prednisone followed by methotrexate and plaquenil. Over the next month, she responded rather dramatically, improving to almost normal muscle strength, although the skin rash on her hand remained. Her prednisone was completely tapered off, and she continued taking a lower dose of methotrexate 15 mg q weekly and plaquenil 200 mg q daily.

A periodic cancer screen was performed due to the diagnosis of DM. About 9 months after the onset of symptoms, a routine colonoscopy, followed by computed tomography (CT) scan identified colon cancer and liver metastasis. A final diagnosis of stage IV moderately differentiated adenocarcinoma of the colon with metastases to the liver and right lower lobe was made. She underwent left hemicolectomy and was started on chemotherapy with FOLFIRI plus bevacizumab. Despite the colon cancer diagnosis, surgery, and chemotherapy, her strength remained fairly stable until 6 months ago, when her weakness returned with severity to the point that she required a wheelchair, experienced severe upper extremity (UE) weakness, and had mild difficulty swallowing. Serum CK was 5,000. She was restarted on steroids at a high dose including one course of intravenous methylprednisolone and methotrexate. Again she responded, although it took several months for improvement to occur. Currently, she continues to note fatigue and is tired after about 4 hours of being up and about. She has some difficulty navigating stairs and experiences an achy feeling in her legs. She is unable to lift heavy packages. Her skin rash has remained unchanged in her hands. Her colon cancer has been stable, and she is continuing with the described chemotherapy along with oxaliplatin.

She has lost about 40 pounds. She notes headaches and fogginess which she attributes to her chemotherapy.

Past History, Family, and Social History

The patient has a history of type 2 diabetes mellitus, hypothyroidism, depression, hypertension, and heart murmur. Past surgeries include caesarean section, cholecystectomy and the colon surgery noted above. Family history is positive for diabetes, hypertension, pancreatic and colon cancer. She is a registered nurse who is now doing secretarial work since she can’t stand on her feet for any length of time. She does not smoke and drinks only socially.

Medication List

The patient’s medications include: esomeprazole 40 mg by mouth once a day; prednisone 5 mg by mouth once a day; desvenlafaxine 50 mg by mouth once a day; hydroxychloroquine 200 mg by mouth once a day; levothyroxine 0.025 mg by mouth once a day; folic acid 1 mg by mouth once a day; olmesartan medoxomil-hydrochlorothiazide 40
mg by mouth once a day; vitamin D 50,000 units by mouth twice a month; risedronate sodium 150 mg by mouth once a month; methotrexate 0.8 cubic centimeters (25 milligram/cubic centimeters) subcutaneously once a week; oxaliplatin every other week; 5-fluorouracil every other week; and bevacizumab every other week.

**Examination**

The patient weighs 153 pounds and is 5 feet 4 inches tall. Blood pressure (BP) 120/86; heart rate (HR) 60. General physical examination is remarkable for a purplish macular rash involving the extensor surfaces of her metacarpophalangeal and interphalangeal joints. Mental status, language functions, and speech were normal. Cranial nerve examination was normal. Muscle strength testing showed weakness (Medical Research Council [MRC] 4/5) strength in the proximal muscles. Distal muscle strength was normal. Quantitative testing is as follows: deltoid 13 pounds on the right, 14 pounds on the left; biceps 30 pounds on the right, 37 pounds on the left; triceps 17 pounds on the right, 23 on the left; wrist extension 17 pounds on the right, 22 on the left; grip 25 pounds bilaterally; iliopsoas 37 pounds on the right, 31 on the left; quadriceps 50 pounds bilaterally; tibialis anterior 50 pounds bilaterally. Sensory examination was normal to pin, vibration, position, and joint sense. Deep tendon reflexes were 2+ and symmetrical with downgoing toes. Mild waddling of gait and difficulty in getting up from low chair was noted.

**Laboratory Testing**

Serum CK is 140. A paraneoplastic panel testing is negative. Sensory and motor nerve conduction studies (NCSs) are normal. Needle electromyography (EMG) shows fibrillations/positive sharp waves (PSWs) (1+) and short duration, small amplitude units with early recruitment in proximal muscles.

**CASE 1: DISCUSSION**

The pattern of weakness in this patient followed the classical symmetrical proximal distribution with lower extremities being more involved than UEs. Cranial muscles were spared except for mild dysphagia. Reflexes were preserved and sensations were normal. Needle EMG showed short duration, small amplitude units in proximal muscles typical of myopathy. Serum CK was elevated x25. ANA was +ve. This constellation of findings of subacute onset is characteristic of myopathy, more specifically inflammatory myopathy. The additional cutaneous manifestations of Gottron sign (small, erythematous papules and plaques on the skin covering the knuckles), erythematous rash in upper back and shoulders (the "shawl sign") and the upper chest (in a V distribution) and telangiectasia at nail beds, were all very typical of DM, despite the lack of typical muscle biopsy findings. She responded to immunosuppressive medications, although the skin manifestation took longer to respond to treatment than the associated myopathy. The clinical presentation followed by malignancy are all typical of a paraneoplastic DM diagnosis.

Paraneoplastic neurological syndromes (PNS) are remote complications of systemic malignancy that cannot be explained directly by the cancer, its metastases, infection, ischemic or metabolic effects. Some PNSs are associated with antibodies against antigens expressed by both the tumor and the nervous system (onconeural antibodies). The presence of these antibodies, the inflammatory response, and the response (in some) to immune modulation suggest that these disorders are immune-mediated. An international panel of neurologists has recommended criteria for diagnosis of suspected PNSs (Table 1).

![Figure 1](Muscle Biopsy)

**Figure 1 Muscle Biopsy**

H & E = hematoxylin and eosin; MHC = major histocompatibility complex; PAS = periodic acid-schiff
Buchbinder and colleagues investigated the risk of malignancy in patients with biopsy proven idiopathic inflammatory myositis; relative risk was 6.2 fold in DM, and 2.0 fold in polymyositis. The mechanisms underlying the association between DM or polymyositis and cancer are not completely understood. The primary antigenic target in DM is the endothelium of the endomysial capillaries, through the C5b-9 membranolytic attack complex. In DM associated with cancer, tumor antigens might be involved and trigger the autoimmune process either through mimicry with endothelium antigens, or via bystander stimulation.

DM may present before, concurrently with, or after the diagnosis of an underlying malignancy. Given the high risk of malignancy in patients with DM (18-45%), and the fact that malignancy may be detected 3 to 5 years after the diagnosis of DM, a high vigil and frequent screening are recommended. The pathogenesis is hypothesized to be oncoproteins expressed on the cancer cells that stimulate an immune response and auto antibodies against the skin and muscle where similar antigens may be present. Treatment of DM in a patient with malignancy involves two approaches: treating the acute inflammatory dermatomyopathy, and treating the underlying malignancy. DM is treated with high-dose corticosteroids, beginning initially with intravenous methylprednisolone followed by oral doses of 60 mg of (1 mg/kg) prednisone. The dose needs to be maintained for at least 1 month and depending on the clinical response, is followed by slow tapering over a period of several months. Steroid sparing agents such as methotrexate are often added to the regimen to help bring down the dose of steroids. The clinical course of DM mirrors the activity of the underlying cancer. A relapse of DM may indicate recurrence of malignancy.

**CASE 2 DESCRIPTION: ATAXIA AND FATIGUE**

**History**

A 63-year-old woman was in her usual state of good health until 6 months prior to presentation when she noted prickling paresthesias in the feet and hands. She also felt increasingly fatigued, and she described episodes of “foggy” vision. She denied any viral illness or any other illness prior to the onset of these symptoms. Her primary care provider did some unspecified blood work, which had normal results. Over the next few months, she developed difficulty walking. She felt wobbly and slow, and tended to turn her left ankle. She noted a loss of fine coordination in the hands. At the same time, she noted a loss of appetite, dry mouth, marked constipation, and weight loss (40 pounds since symptom onset). Tingling and numbness, which originated in the toes, now extends to the left thigh and in the right leg up to the knee.

When she stands, she feels lightheaded and diffusely weak. Her husband documented her systolic blood pressure in the 60s when standing.

**Past Medical and Social History**

The patient smoked three packs of cigarettes per day from 1958 to 2003, and drank up to six beers per day from 2006 to 2008. She no longer smokes or drinks alcohol. The patient worked as a school teacher and homemaker.

**Examination**

Generally, she looks unwell and thin, but is in no distress. Mental status is normal. Vitals: supine BP 133/70, HR 98; standing (3 min) BP 61/41, HR 106.

Speech is normal and cranial nerve examination is normal. No nystagmus or dysarthria.
The imbalance and incoordination appear to be diffuse reduction in power. Tendon reflexes are absent throughout.

On sensory examination, there is reduced pin sensation to the ankles and wrists. Vibration and joint position sensation is absent at the toes, ankles, and fingertips, and reduced at the wrists. Gait is wide based and unsteady. Romberg sign is present. With arms outstretched, there are slow, drifting movements of the fingers and hands (these movements increase in amplitude with eyes closed). Finger to nose testing is imprecise, and rapid alternating movements are slowed.

**Electrophysiological Studies**

Motor NCSs are normal in the left arm and leg. Repetitive (3Hz) stimulation of the left ulnar nerve produced no decrement. Median and sural sensory responses are absent bilaterally. The ulnar sensory response is 8µV on the left and 25µV on the right. The left radial sensory amplitude is 5µV. Distal sensory latencies (where obtained) are normal. Trigeminal blink reflex responses are normal. Needle examination is normal.

**Laboratory Studies**

Normal results for angiotensin converting enzyme, c-reactive protein, basic metabolic panel, B12, B6, thiamine, lipid panel, SPEP, fasting glucose, hepatitis serologies, Lyme immunoglobulin G (IgG), ANA, anti-neutrophil cytoplasmic antibodies, Sjögren syndrome (SS)A/B, human immunodeficiency virus, urine metals (arsenic, cadmium, lead, mercury), and serum copper.

Complete Blood Count showed Hgb 9.4, but was otherwise normal. Sedimentation rate (33) is mildly elevated.

Cerebrospinal fluid (CSF) examination: protein 59, 3 White Blood Count/mm3, normal IgG index and synthesis rate, and 8 oligoclonal bands (high).

Paraneoplastic antibody studies: anti-neuronal antibody type 1 (ANNA-1) (anti-Hu) positive 1:256 in CSF, 1:15,360 in serum.

**Imaging Studies**

Magnetic resonance imaging (MRI) brain – normal

CT chest – pleural thickening in the left lower lobe. Enlarged mediastinal lymph node.

Bronchoscopy – non-diagnostic

Mediastinal biopsy – lymph node with one granulomatous focus, no malignancy.

**CASE 2: DIFFERENTIAL DIAGNOSIS**

The first challenge in this case is to correctly localize and identify the nature of the neurological deficits. The imbalance and incoordination of the hands was initially considered to be a cerebellar ataxia; however, careful clinical examination revealed marked loss of proprioception in the limbs causing sensory ataxia. Although the Romberg sign is a useful indicator of proprioceptive loss in the lower limbs, this sign (loss of balance when visual cues are removed) can also be present in cerebellar disorders. The patient’s complaints of sensory loss and paresthesias also point to a problem in sensory pathways. Clinically, large fiber sensory modalities (vibration and joint position) are more severely affected than small fiber modalities (pain and temperature). Areflexia, in this case, results from the loss of muscle spindle (large fiber) afferents.

Severe proprioceptive loss will limit the patient’s ability to properly coordinate muscle contraction and lead to the impression that muscle power is reduced. One clue that may be present is an improvement in muscle strength if the patient is directed to look at the joint that is being tested. Another clue to a severe proprioceptive disturbance is the appearance of pseudoathetosis (a slow writhing movement, usually seen in the fingers, that develops when the patient is not looking at the limb). The asymmetric selective damage to large fiber sensory modalities could relate to a problem at the level of the dorsal root ganglia (a neuronopathy) or a more rostral problem in posterior columns. A peripheral disorder is confirmed by the abnormal sensory NCSs with completely normal motor responses.

In addition to sensory neuropathy, the patient has symptoms of diffuse autonomic failure affecting sympathetic function (causing orthostatic hypotension), parasympathetic function (dry mouth) and gastrointestinal motility (constipation). Gastroparesis can produce nausea and early satiety, and this may contribute to the marked weight loss in this patient. Patients with orthostatic hypotension may not give a typical description of lightheadedness with standing, but instead, may complain of fatigue, blurry vision, headache, or neck pain.

**Paraneoplastic Sensory Neuronopathy**

Paraneoplastic syndromes are complications of cancer that cannot be attributed to direct effects of the neoplasm or its metastases. Peripheral neuropathy is arguably the most common paraneoplastic syndrome and may present well in advance of a cancer diagnosis. In many cases, the characteristics of a paraneoplastic peripheral neuropathy are those of a mixed sensory and motor length dependent axonal neuropathy indistinguishable from the nonparaneoplastic neuropathies commonly encountered in neurology clinics. A few clinical features should heighten the clinical suspicion. The onset of paraneoplastic neuropathy tends to be more rapid with progression of symptoms, signs, and electrophysiological changes over weeks or months. Pain is typical. Analysis of CSF may show mild abnormalities. Peripheral neuropathy has been associated with a number of cancers (small cell and nonsmall-cell lung cancer, breast cancer, and thymoma) and with several autoantibody markers (Table 2). However, antibody studies may be negative in many patients with paraneoplastic peripheral sensorimotor neuropathy.

**Small Cell Lung Cancer**

Progressive neuropathy that exclusively affects the sensory nerves has been termed pure sensory neuropathy, sensory ganglion-
Usual Tumor Commonly associated syndromes

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Usual Tumor</th>
<th>Commonly associated syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANNA-1 (anti-Hu)³</td>
<td>SCLC</td>
<td>Limbic encephalitis, ataxia, sensory neuronopathy, autonomic and sensorimotor neuropathies</td>
</tr>
<tr>
<td>CRMP-5 (anti-CV2)⁴</td>
<td>SCLC or thymoma</td>
<td>Encephalomyelitis, chorea, neuropathy, optic neuritis</td>
</tr>
<tr>
<td>Amphiphysin</td>
<td>Lung or breast cancer</td>
<td>Encephalomyelitis, neuropathy, &quot;stiff-person syndrome&quot;</td>
</tr>
<tr>
<td>ANNA-2 (anti-Ri)</td>
<td>Lung or breast cancer</td>
<td>Ataxia, opsoclonus-myoclonus, neuropathy</td>
</tr>
<tr>
<td>N-type calcium channel antibodies</td>
<td>Lung or breast cancer</td>
<td>Peripheral neuropathy and many other syndromes</td>
</tr>
</tbody>
</table>

* Alternate nomenclature is indicated in parentheses
ANNA = antineuronal antibody type 1; CRMP-5 = collapsin response mediator protein; SCLC = small cell lung cancer

Paraneoplastic syndromes are thought to be autoimmune disorders caused by an immune response against cancer. Onconeural antigens expressed by the tumor cells cause the immune system to become misdirected against components of the nervous system. Paraneoplastic neurological disorders can involve any part of the nervous system and may affect multiple areas simultaneously. The diagnosis of cancer may be difficult because the cancers are often small in size and limited in spread. If CT imaging is negative, diagnostic yield may be increased by positron emission tomography (PET) scan (especially in cases with positive paraneoplastic antibodies and therefore high clinical suspicion). If initial cancer screening is negative, repeat studies at close intervals is appropriate. Despite the normal imaging and biopsy, the patient will return in 3 months for CT and PET imaging with fluorodeoxyglucose of the chest.

There are no proven therapies for paraneoplastic neurological syndromes such as PSN, although there have been several small open label treatment series using intravenous immunoglobulin, plasma exchange, corticosteroids, cyclophosphamide, or a combination of these. Treatment generally consists of identification and aggressive management of the associated malignancy along with consideration of immunomodulatory therapy. Since the underlying pathology involves destruction of the sensory neurons, dramatic improvement is not expected.

**Paraneoplastic Autonomic Neuropathy**

Paraneoplastic autonomic neuropathy typically presents as a subacute panautonomic neuropathy. Limited presentations may also occur, most notably severe gastrointestinal dysmotility without other autonomic features (paraneoplastic enteric neuropathy). As with other paraneoplastic disorders, the symptoms usually precede the diagnosis of cancer, and the tumors, when found, are limited in stage or only locally metastatic (regional lymph nodes).

The time course of paraneoplastic autonomic neuropathy varies from acute autonomic failure to a more insidious onset over several months. Orthostatic hypotension and anhidrosis (dry skin and/or heat intolerance) reflect sympathetic failure. Parasympathetic failure manifests as impaired cardiovagal function (tachycardia and impaired heart rate response to deep breathing, Valsalva or standing), erectile dysfunction, dry eyes and mouth, and/or dilated and poorly reactive pupils. Patients may have bladder dysfunction, although there is no consistent pattern to the urinary complaints. Gastrointestinal complaints are very common, usually consisting of severe constipation, gastroparesis, or intestinal pseudoobstruction. Even if the time course is unclear, the presence of pupillary abnormalities and prominent gastrointestinal symptoms help distinguish autoimmune and paraneoplastic autonomic neuropathies from more chronic degenerative autonomic disorders.

When subacute autonomic failure develops in combination with another peripheral or central neurological syndrome, paraneoplastic disease should rise to the top of the differential diagnosis. The auto antibody most commonly associated with paraneoplastic autonomic neuropathy is anti-Hu, (ANNA-1). SCLC is found in more than 80% of patients who are seropositive for ANNA-1.³ This antibody recognizes a family of 35 to 40 kDa neuronal nuclear ribonucleic acid-binding proteins and labels the nuclei (and to a lesser extent, the cytoplasm) of all neurons. Characteristically, ANNA-1 also binds to peripheral neurons in autonomic ganglia, dorsal root ganglia, and myenteric plexus.
Treatment of paraneoplastic autonomic neuropathy generally consists of supportive symptomatic treatments to alleviate the most problematic symptoms, orthostatic hypotension, and gastrointestinal dysmotility. Every effort should be made to locate and treat the underlying malignancy. In some cases, autonomic function improves once the malignancy is effectively treated. Plasma exchange or intravenous immunoglobulin have also been effective in individual reports. Nevertheless, even with prompt diagnosis and appropriate treatment, many patients are left with some degree of residual autonomic deficits.

Sensory and Autonomic Neuropathy with Sjögren/sicca Syndrome

The exact frequency of neuropathy associated with primary SS is unknown but estimated to be about 10%. A variety of neuropathies can be encountered, and neuropathy may be the initial presentation. Similar patterns of neuropathy may be encountered in patients with sicca syndrome (dry eyes and dry mouth) that do not fulfill diagnostic criteria for SS.9 Sensory neuropathy is the most common presentation, usually a painful distal small fiber neuropathy. Sensory ganglionopathy with sensory ataxia and trigeminal sensory loss is a distinctive but uncommon presentation. The involvement of the trigeminal sensory nerve (which can be identified clinically or electrophysiologically) may help distinguish this form of sensory ganglionopathy from PSN. Autonomic features are often present in association with the sensory neuropathy, characterized by sweating abnormalities and constipation. In a minority of cases, tonic unresponsive pupils can occur. Preliminary studies have suggested that antibodies against muscarinic acetylcholine receptors may be associated with the autonomic neuropathy of SS.10

Other less common neuropathic manifestations of SS include isolated trigeminal sensory neuropathy, multiple cranial neuropathies, or vasculitis with mononeuritis multiplex. CNS manifestations (including myelitis) can also be associated with SS.

Diagnosis consists of symptoms and objective evidence of dry mouth and dry eyes along with confirmatory salivary gland biopsy showing inflammation or presence of antibodies. The antibodies that are most closely associated with SS are anti-Ro/SS-A and anti-La/SS-B. These antibodies are found in about 60% of patients with SS. Other serological findings include anti neuronal antibodies or rheumatoid factor.

Treatment of sensory neuropathy associated with SS is often unsatisfactory.11 Corticosteroids, hydroxychloroquine, and other agents have been used. Fortunately, the sensory ganglionopathy in SS is not as severe as that of PSN, and patients typically do not lose the ability to ambulate. Likewise, autonomic deficits are milder than in paraneoplastic autonomic neuropathy and consist mainly of “cholinergic” dysfunction (reduced secretomotor function and constipation) which can be managed symptomatically. The severity of sensory and autonomic deficits in this patient and the lack of serological markers of SS make this diagnosis much less likely than PSN.

Anti-myelin-associated Glycoprotein Sensory Neuropathy

Monoclonal gammopathy and antibodies against various peripheral nerve antigens can be associated with neuropathy, many of which are demyelinating. Approximately 50% of patients with neuropathy and IgM gammopathy have IgM autoantibodies to myelin-associated glycoprotein (MAG).12 Anti-MAG auto antibodies often cross react with other peripheral nerve glycolipids, including (3-sulfated glucuronyl paragloboside), and sulfated glucuronyl lactosaminylparagloboside, which share an antigenic carbohydrate determinant with MAG.

The typical clinical presentation of the neuropathy associated with anti-MAG antibodies is a slowly progressive, distal, symmetric predominantly sensory or sensorimotor PN.13 Most patients are male. The neuropathy begins with sensory symptoms, and approximately 75% of patients present with paresthesias.12 Large fiber sensory deficits can be severe. Gait ataxia presents a major disability in one third of patients, and hand tremor is commonly observed. Over time the majority of patients develop motor nerve involvement with primarily distal weakness. The legs are usually affected more than the arms. Deep tendon reflexes are usually reduced or absent.

On laboratory testing, an IgM paraprotein is found in approximately 50% of cases on serum protein electrophoresis and immunofixation studies, typically with a kappa light chain. NCSs usually demonstrate demyelination. Prolonged distal motor latencies are the most reliable finding, seen in 90% of patients. Neuropathy associated with IgM gammopathy but no anti-MAG activity may be clinically indistinguishable from the anti-MAG neuropathy. A positive anti-MAG assay confirmed by Western blot is strongly suggestive of an immune-mediated PN, usually associated with an IgM paraprotein. Immunotherapy regimens may be attempted in patients with significant neurologic impairment, although the treatment response is often disappointing. The presence of an IgM paraprotein should prompt a workup for an underlying plasma cell dyscrasia. Although anti-MAG neuropathy can present as a sensory ataxia, our patient did not have evidence of demyelination (normal distal latencies) and did not have a monoclonal gammopathy.

REFERENCES for Case 1


REFERENCES for Case 2
Boy With Weakness

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CASE DESCRIPTION

History

A 5-year-old boy presented with clumsiness, gait abnormality with toe walking, frequent falls, difficulty going up stairs, difficulty getting up from the floor, and was also the slowest runner in his class. Gestation was reportedly normal, and he was born without any significant medical problems, and with good muscle tone. He was mildly delayed in achieving motor developmental milestones, and ambulation was delayed until 18 months. His primary care physician noted that his calf muscles were somewhat large. His parents reported that the patient frequently complained of aches in his calves. Past medical history was otherwise unremarkable. There was no family history of any neuromuscular disorders causing similar symptoms, and specifically there was no family history of either Duchenne or Becker muscular dystrophy (DMD/BMD).

Physical examination revealed an otherwise normal appearing boy with normal mental status, normal and symmetric cranial nerve examination, with good facial muscle strength. No tongue atrophy or fasciculation were noted, but it seemed to be somewhat enlarged. Cardiopulmonary and abdominal examination was otherwise unremarkable. Inspection of his shoulder girdle revealed posterior axillary fold depression and his bilateral calf muscles were markedly enlarged. Motor strength examination revealed neck flexion weakness, as well as proximal shoulder and pelvic girdle weakness with relatively good distal strength. Sensation was intact throughout. Deep tendon reflexes were 2+ and symmetric at his knees but absent at the ankles. His heel cords were tight bilaterally and his ankles did not achieve neutral dorsiflexed position. The patient displayed a Gower maneuver when attempting to stand from a seated position on the floor. His standing posture revealed mildly swayed back and shoulders with lumbar hyperlordosis. His gait pattern was mildly broad based.
with bilateral Trendelenburg’s sign with waddling gait and toe walking. Initial laboratory studies with the pediatrician revealed increased aspartate aminotransferase (438 U/L) and alanine aminotransferase (635 U/L), but normal gamma-glutamyl transpeptidase (8 U/L), increased lactate dehydrogenase (1786 U/L), and creatine kinase (CK) > 22,000 U/L. Reportedly, the patient underwent deoxyribonucleic acid (DNA) testing for DMD and BMD, but the results returned negative.

DIFFERENTIAL DIAGNOSIS

A broad differential diagnoses exist for childhood-onset weakness and myopathy. However, this particular patient’s history, physical examination, and laboratory results are highly suggestive of a muscle disorder with a significant amount of inflammation and degeneration. The differential diagnoses given such a high CK with significant weakness is quite limited, and with common things being common, dystrophinopathies (either DMD/BMD) top the list. However, there are a few other diseases that can mimic such a clinical and laboratory presentation that should be considered in the differential diagnoses.

Limb girdle muscular dystrophies (LGMD), especially the autosomal recessive LGMDs including dysferlinopathy (LGMD 2B, or Miyoshi myopathy) and sarcoglycanopathies (LGMD 2C-F), can often have very high CK and should be considered. The clinical presentation and phenotype of LGMD 2C (also previously called severe childhood autosomal recessive muscular dystrophy, SCARMD) can be especially similar to DMD/BMD. LGMD 2C is due to mutations in γ-sarcoglycan gene and can show similar age of symptom onset as our patient, as well as physical findings including proximal greater than distal weakness, calf pseudohypertrophy, myopathic gait, and Gower sign. The other sarcoglycanopathies can also present similarly to our case patient: LGMD 2D (α-sarcoglycan), LGMD 2E (β-sarcoglycan), LGMD 2F (δ-sarcoglycan). Although the CK can be very high in the range of dystrophinopathy, muscle biopsy staining for specific sarcoglycan abnormalities will be helpful in diagnosis and in differentiating sarcoglycanopathies from each other and from dystrophinopathies (DMD/BMD). LGMD 2B (dysferlin) typically presents later in childhood and in early adulthood, but also shows a very high CK. Dysferlinopathy may show pseudohypertrophy of calves early in disease course, but as the disease progresses, calves are actually atrophied. Other autosomal and recessive LGMDs are also in the differential but less likely based on age of onset and the degree of CK elevation; they typically tend to present later in life and with moderately elevated CK instead of the very high CK noted in our case patient.

Acid maltase deficiency (Glycogenosis Type 2, Pompe disease) should also be included in the differential diagnoses. It is an autosomal recessive disease that results in either reduced or absent acid maltase (acid α-glucosidase [GAA]) enzyme activity throughout the body. GAA enzyme hydrolyzes lysosomal glycogen. The severity and onset is dictated by the level of residual GAA enzyme activity; the lower the enzymatic activity, the earlier the onset and more severe the phenotype. In the infantile form with absent enzyme function, there is severe hypotonia and weakness, and associated significant systemic, cardiac, pulmonary, and hepatic abnormalities that often result in death before 1 year of age. However, the late-onset forms of Pompe disease (childhood and adult forms) display milder phenotype due to residual (2-6%) GAA enzyme activity. The age of onset varies but can be as early as 1 year of age. Proximal weakness is noted with calf pseudohypertrophy, and occasional tongue enlargement can be also appreciated. There appears to be less cardiac involvement but pulmonary function is decreased and usually is the cause for death as the disease progresses. Since now there is an enzyme replacement therapy available, it is important to consider and diagnose Pompe disease early.

Inflammatory myopathy can present with a very high CK as seen in this patient. Juvenile dermatomyositis has a history of skin rash that can help in diagnosis, although this history can be difficult to elicit. Vascular changes at nailbeds, calcinosis, and Gottron’s papules over extensor digit surfaces or elbow joints may be present. Joint and muscle pain are usually significant complaints in addition to weakness. Also the history will reflect achievement of normal motor milestones until a relatively acute onset and progression of weakness. CK can be very high in the range of dystrophinopathy, and associated elevation in aldolase is also noted.

Congenital muscular dystrophies are a group of hereditary muscle diseases that present with hypotonia in infants and sometimes with contractures. Typically the patients are severely affected and cannot walk, or if ambulating achieve walking very late around 2-3 years. Both syndromic and nonsyndromic forms typically have central nervous system manifestations with abnormalities on magnetic resonance imaging and sometimes with seizure disorders. Some forms show joint laxity and later progress to contractures. CK can be moderately elevated but usually not to the degree seen in this case.

Myotonic muscular dystrophy shows an autosomal dominant pattern of inheritance, often with typical facial features. Clinical myotonia, either percussion or grip, is the hallmark and needle electromyography (EMG) will show myotonic discharges. Frequently, there are also cardiac conduction abnormalities, increased incidence of catacacts and insulin resistance, but these are typically present later in the course of the disease. CK can be moderately elevated, but usually not to the degree seen in this patient or in dystrophinopathy.

There are other muscle diseases that are less likely. Congenital myopathies are unlikely given that the patient did not have low tone or hypotonia during early infancy, or significantly delayed milestones. Congenital myopathies also typically are either static or improve in terms of strength as the child grows, and CK is usually either normal or slightly high, but not to the degree seen in DMD/BMD. Morphological findings on muscle biopsy are usually helpful in distinguishing types of congenital myopathies. Emery Dreifuss muscular dystrophy has an X-linked form (emerin) with CK elevation that can be high, but usually less than 10x normal range, and contractures at elbows and tight heel cords are usually present before appreciable weakness. Fascioscapulohumeral muscular dystrophy (FSHD) is usually later in onset but can present as a congenital form or in childhood. Significant facial weakness is noted that helps to differentiate it from other myopathies. Shoulder girdle weakness is
prominent and typically presents earlier than the lower limb or pelvic weakness. In the infantile form of FSHD, there is often an associated sensorineural hearing loss, retinal telangiectasia, mental retardation or seizures (Coat’s). CK is either normal or moderately elevated but typically < 5x normal.

EVALUATION & UPDATE

DMD/BMD are still the most likely diagnoses even though there is no family history (as much as a third of cases are due to a de novo mutation) and the preliminary genetic testing came back negative (deletion/duplication analysis can be negative and miss point mutations). It is by far the most common childhood onset muscular dystrophy, and when symptoms are present, especially in a boy with a very high CK, clinical suspicion is raised and additional testing should be pursued. For this patient, a muscle biopsy was ordered for diagnostic purposes, and showed morphological findings consistent with a significant muscular dystrophy, with absent dystrophin staining. Western blot analysis revealed essentially absent dystrophin protein (<3%) consistent with the diagnosis of DMD. For this patient, a few years later when dystrophin gene sequencing analysis became available, a subsequent DNA sequencing revealed a premature stop codon in exon 55. The patient participated in a PTC124 clinical trial.

Dystrophinopathy Testing Strategy

In the past, muscle biopsy and electrodiagnostic evaluations were utilized more for diagnostic purposes in dystrophinopathies. However, with the advances in molecular genetic diagnostic technologies, in an appropriate clinical context, dystrophin gene DNA testing is now the preferred method and often the first step in working up DMD/BMD. At this time, current combination of dystrophin genetic testing methods approach 99% sensitivity in picking up a disease causing mutation. Deletions account for a majority of mutations found in DMD (~65%) and BMD (~85%), while point mutations and splicing mutations (~25-30%) and duplications (~5-10%) account for the remainder (1-5%). In addition, it is estimated that a premature stop codon point mutation accounts for about 13-15% of mutations. Since the dystrophin gene is large and deletions account for a major proportion of mutations, typical genetic testing strategy is to perform deletion/duplication analysis first, and then proceed to a sequencing study when no deletion/duplication is detected. There has been an effort to put together a database of mutations and correlations to phenotype, and while some prediction can be made based on genetic mutation, ultimately the clinical progression and analysis of dystrophin protein are more closely linked with the phenotype. Mutation analysis of BMD has shown that the majority are "in-frame" deletions while DMD results from "frameshift" mutations. Muscle biopsy is an invasive procedure with a reported complication rate of about 1%, but aside from that it is additionally stressful for a child. At this time, in rare cases when no disease causing mutation can be found, a muscle biopsy is performed for immunohistochemical analysis and Western blot for quantitative analysis of dystrophin protein. Clinically, even in some cases with confirmed dystrophin gene mutation, a muscle biopsy can be helpful with atypical phenotype presentations and in formulating prognosis via immunohistochemical and Western blot analysis: approximate phenotype prediction based on dystrophin quantity: <5% DMD; 5-20% outlier DMD or severe BMD; and >20% BMD. Once the proband genetic mutation is identified, the family should be referred for genetic counseling, and DNA or linkage studies of mother and siblings can be considered.

Duchenne Muscular Dystrophy

DMD is the most common form of childhood muscular dystrophy, with an incidence of approximately 1:3,500 male births. DMD is an X-linked disorder with the chromosomal abnormality at the Xp21 gene locus, with mutations in the dystrophin gene.1,2 The dystrophin protein plays an important role in dystrophin-associated glycoprotein complex (DGC) and is thought to be a major cytoskeletal component of the muscle cell membrane. It appears that absence of dystrophin makes the muscle cell highly susceptible to mechanical stress, with eventual muscle fiber loss and replacement with fibrotic tissue. Dystrophin is also thought to play an important role in muscle cell signaling pathways.

Although a family history is typical, as many as one-third of cases may be due to new mutations, without any previous family history. Typical initial symptoms include abnormal gait, frequent falls, and difficulty climbing steps. Hypotonia and delayed motor milestones occur in earlier onset cases, but in 75% to 80% of cases, onset is noted before age 4. The abnormal gait is often noted by toe-walking, which is a compensatory adaptation to knee extensor weakness, or increased lumbar lordosis as a compensation for hip extensor weakness. Another indication of pelvic girdle weakness is Gower sign. CK is typically at least 10-20x normal, but often as high as 50-200x normal and peaks at about age 2-3 years.

On examination, the earliest weakness is seen in the neck flexors, typically during the preschool years. Weakness of the proximal musculature of the shoulder and pelvic girdle is next, with steady progression, although the patient and family may feel that functional loss does not occur gradually, but rather quite suddenly. This may relate to a critical point in weakness when compensatory actions can no longer suffice to perform a task. Quantitative strength testing shows greater than 40 to 50% loss of strength by age 6 years, with fairly linear progression from ages 5 to 13 measured by manual muscle testing.6 In patients not treated with corticosteroids, the average age to wheelchair use is 10, with a range of 7 to 13 years of age. Prediction of transition to wheelchair use may be helped by using timed motor performance tests. In a natural history study conducted at the University of California Davis, all DMD subjects who took more than 12 seconds to ambulate 30 feet lost the ability to ambulate within 1 year.6 Immobilization, even for an acute illness, may lead to permanent loss of ambulatory ability during this phase of the disease. In addition, respiratory insufficiency, cardiac dysfunction, contractures, scoliosis, cognitive, and nutritional issues also complicate the care of DMD patients. Historically, the life expectancy has been from the late teens to early 20s, although with improved pulmonary care, patients with
DMD are living longer, with the average life expectancy increased from 19 to 25 years, and increasing numbers of patients living into their thirties. The leading cause of death is respiratory insufficiency and a minority (~20%) of deaths are felt to be due to cardiac complications.

**Becker Muscular Dystrophy**

BMD represents a milder phenotype than DMD. In the case of BMD, dystrophin levels can range from 20 to 80% of normal, or have the presence of the protein with an abnormal molecular weight. BMD is less common than DMD, with an overall prevalence of about 1:18,000-35,000 male births. It has a similar pattern of muscle weakness, but generally presents with a later onset and a slower rate of progression. Without dystrophin immunohistochemical analysis, it may be difficult to clinically discriminate between DMD and BMD. Although age of onset typically occurs later in BMD, there is significant overlap with DMD. Nor does the degree of CK elevation discriminate between the two diseases. The most useful clinical diagnostic discriminator is the ability to ambulate into adolescence. It is unusual for a patient with BMD to be wheelchair dependent before late adolescence, whereas even DMD outliers are dependent on the wheelchair for mobility by age 16. In fact, some BMD patients may be ambulatory well into middle age and beyond. Significant scoliosis is much less common than in DMD, and rarely requires spinal instrumentation. One particular clinical concern in BMD is the potential for significant cardiac disease out of proportion to other manifestations of the myopathy. ECG abnormalities can be detected in about 75% of BMD patients. Echocardiography demonstrates left ventricular dilatation in 37% of BMD patients, and 63% have subnormal systolic function that is due to global cardiac hypokinesia. Cardiac transplantation may even be necessary in some patients. The degree of cardiac compromise may not be reflected by clinical symptoms, and these patients should be screened at regular intervals with electrocardiogram (ECG) and echocardiographic (TTE) studies. Unlike DMD, significant pulmonary dysfunction is not a hallmark of BMD but may occur later in the disease course.

**MANAGEMENT ISSUES**

The care of DMD patients is best coordinated within a multidisciplinary team approach since many different specialists with expertise in different clinical areas are required (Table 1).

**Cardiac Issues**

It is not surprising that cardiac function is affected in DMD, because the dystrophin protein has been shown to be present in both the myocardium and Purkinje fibers. Subclinical cardiac involvement is seen in about 25% of patients less than 6 years of age, with persistent tachycardia as the most common finding. Cardiomyopathy is usually noted after 10 years of age with about one third clinically apparent by age 14, and occurs in nearly all patients by age 18. By age 13, most DMD patients also demonstrate ECG abnormalities. The first abnormalities noted are Q-waves in the lateral leads, followed by elevated ST segments, poor R-wave progression, increased R/S ratio, and resting tachycardia and conduction defects. Sudden death from ventricular ectopy and left ventricular dysfunction, can be present in DMD. However, dilated cardiomyopathy and progressive congestive heart failure are the more frequent sequelae. Clinical and TTE onset of systolic dysfunction is associated with a poor short-term prognosis.

In terms of guidelines for surveillance, before age 10 a baseline ECG and TTE should be obtained and followed every 2 year. After 10 years of age, ECG and TTE are recommended every year, with addition of a Holter monitor when cardiac rhythm abnormality is suspected and at the discretion of the cardiologist. The management of cardiac complications in DMD often starts with low dose angiotensin converting enzyme inhibitors (ACEI); these are usually initiated when the measured ejection fraction falls below 35-40%. However, there now appears to be some evidence supporting earlier initiation of ACEI to improve cardiac function. There is an increasing trend to initiate low dose ACEI earlier with the thought that it may improve ventricular function through cardiac remodeling mechanisms; however, further studies are needed for optimal cardiac management in DMD. Beta blockers, digitalis, and antiarrhythmics may also have a role in DMD.

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ADLs = activities of daily living; DMD = Duchenne Muscular Dystrophy

**Pulmonary issues**

In DMD, pulmonary complications are the leading cause of death. Progressive respiratory muscle weakness in DMD leads to restrictive lung disease manifesting as hypoventilation, hypercarbia, sleep disordered breathing, and ultimately respiratory failure. The causes of respiratory failure include direct respiratory muscle involvement from the skeletal myopathy, alteration in respiratory mechanics, poor secretion management, infections, and occasionally a problem with central control of respiration.
Monitoring of respiratory function using pulmonary function tests (spirometric measures) should begin around age 7 or 8, and before transition to wheelchair. Before the age of 5, it is difficult to obtain reliable spirometry measurements due to poor cooperation by the child. This author and colleagues, typically obtain serial oxyhemoglobin saturation, forced vital capacity (FVC), forced expiratory volume, maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), and peak cough flow measures every 3-12 months based on severity of pulmonary dysfunction. Signs and symptoms suggesting respiratory impairment include those related to sleep-disordered breathing (nightmares, morning headache, and daytime drowsiness), as well as respiratory dysfunction (exertional dyspnea, orthopnea, generalized fatigue, and paradoxical breathing patterns). A polysomnography with continuous carbon dioxide (CO2) monitoring is helpful in determining sleep-related hypoventilation associated with DMD. 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 either unavailable, or not convenient for patient. Screening for sleep disordered breathing and nocturnal alveolar hypoventilation should be done every year typically after transition to wheelchair. Improved pulmonary toilet and clearance of secretions can be achieved with assisted cough, deep breathing and set-up spirometry, percussion and postural drainage, portable suction machine, and in more severe cases, the additional use of intrapulmonary percussive ventilation (IPPV), and in-exsufflator (cough assist) machine. Other general measures for patients with restrictive lung disease include yearly influenza vaccination and a pneumococcal vaccination unless there are contraindications.

Measurements of respiratory function have allowed clinicians to better determine the need for ventilation and cough assistance. Serial FVC measurements are highly predictive of respiratory impairment and survival. A FVC of less than 1 liter has shown to be the best negative predictor of survival in DMD, with mean survival of 3.1 years and 5 year survival of approximately 8% if ventilatory support is not provided. The absolute FVC volumes increase concomitant with growth between 5-10 years of age with percent predicted FVC remaining relatively stable and close to 100% predicted. A linear decline at a rate of about 10% per year in percent predicted FVC typically occurs between 10-20 years of age. In the most severe DMD cases, the maximal FVC reached a plateau of less than 1200 ml. This was associated with loss of ability to walk before age 10 and severe progressive scoliosis. Moderately severe DMD cases with respiratory compromise reached maximal FVC between 1200 ml and 1700 ml. The least severe DMD cases reached plateaus in FVC of greater than 1700 ml. Similarly, those patients with highest peak FVC achieved (> 2500 ml) had a milder disease progression. Thus, the peak obtained absolute values of FVC usually occurring in the early part of the second decade is an important prognostic indicator for ultimate severity of restrictive pulmonary compromise. Other spirometric measurements including MIP, MEP, and peak cough flow are also useful. When these values decline (peak cough flow less than 160 L/min or MEP less than 45 cm H2O), they can indicate poor airway clearance function and hastened respiratory failure. Manual techniques or mechanical insufflator-exsufflators (cough-assist machines) can help improve airway clearance and secretion management.

Nocturnal noninvasive intermittent positive pressure ventilation (NIPPV) is an effective treatment for DMD patients with restrictive lung disease. NIPPV may be delivered via mouthpiece with or without a lip seal, via nasal mask, or full-face mask. Nocturnal NIPPV with bi-level positive airway pressure (BiPAP) has demonstrated its efficacy in use with sleep-disordered breathing and night-time hypoventilation in DMD. In general, BiPAP mode of ventilation rather than continuous positive airway pressure (CPAP) is appropriate for the majority of restrictive pulmonary processes seen with myopathies. Frequent monitoring for adequate mask fit and appropriate ventilator pressure level settings is necessary. Early initiation of NIPPV is advocated by some and is increasing in its support. Guidelines as to when to initiate NIPPV vary, and some have recommended to start with a partial pressure of carbon dioxide (PaCO2) ≤ 45 mm Hg. However, most would agree that symptoms of respiratory distress or the presence of nocturnal hypoventilation are certainly indications for NIPPV. We suggest considering NIPPV initiation when the supine FVC falls below 50% of predicted values, depending on the clinical symptomatology. The rate of the patient’s disease progression must also be considered in deciding when to initiate NIPPV. Initially, NIPPV is used only at night. As patients continue to lose vital capacity, ventilator use extends into the day for varying periods and eventually becomes 24 hours continuously.

Ventilatory support has been shown to prolong survival and improve quality of life in DMD. The long-term use of noninvasive ventilation is associated with fewer complications than ventilation via a tracheostomy. Continuous invasive ventilatory support via tracheostomy can be considered when respiratory dysfunction progresses despite noninvasive ventilation. Decisions regarding invasive ventilation are often difficult and ideally should be started early in the disease process. Patients and families should be educated about available ventilator and palliative options, and discussion about advanced directives and respiratory management should continue as the disease progresses.

Contractures

Joint contractures are a major concern in DMD. Nearly all affected boys older than 13 years have contractures, and they are almost always associated with transition to wheelchair. They most commonly occur first in the ankle plantar flexors, iliobibial bands, and hip flexors, with subsequent involvement of the knee flexors, and elbow and wrist flexors. There does not appear to be a strong correlation between less than antigravity strength for a muscle group and the severity of joint contracture, nor for strength imbalance between antagonists across a joint. Clearly, lower-extremity contractures become a problem after transition to a wheelchair for a significant part of the day. Significant lower-extremity contractures also develop after transition to wheelchair. Natural history data suggest that progressive weakness, rather than heel-cord contractures, is associated with loss of ambulation as plantar-flexion contractures greater than 15 degrees are uncommon until after wheelchair reliance. Principle therapy modalities including stretching and appropriate use of splints must be done regularly to prevent or delay the development of contractures for those at risk for musculoskeletal deformity. Bracing and
surgical management of contractures may help prolong ambulation in DMD. In this population, the late phase of ambulation often is associated with more marked joint contractures involving the iliobial bands and heel cords, because DMD patients spend more time sitting and less time standing. The release of contractures at both the heel cord and iliobial band generally is necessary to obtain successful knee, ankle, foot, orthesis (KAFO) bracing. The ankle deformity may be corrected by either a tendo-achilles lengthening (TAL) or a TAL combined with a surgical transfer of the posterior tibialis muscle tendon to the dorsum of the foot. The posterior tibialis tendon transfer corrects the equinovarus deformity, but prolongs the time in a cast and recovery time, and it increases the risks of prolonged sitting.

**Scoliosis**

Scoliosis is a major clinical concern in DMD, and prevalence is strongly related to age. Fifty percent of DMD patients acquire scoliosis between ages 12-15. About 10% of DMD subjects show no significant clinical spinal deformity. The rate of progression of the primary or single untreated lateral curve has been reported to range from 11 degrees to 42 degrees per year, depending on the age span studied. Although significant curves often coincide with transition into wheelchair mobility, there does not appear to be a cause-and-effect relationship between scoliosis and wheelchair use. Rather, factors such as the adolescent growth spurt and progressive involvement of the trunk musculature may be responsible for progression of scoliosis during the adolescent years. There is some evidence that severity of scoliosis may be predicted by the type of curve and early pulmonary function measurements. When the curves do not involve significant kyphosis or hyperlordosis and peak FVC is greater than 2 liters, severe progressive scoliosis appears less likely. It is clear that bracing does not slow the progression of spinal deformity.

Close clinical monitoring is essential for boys with DMD at risk for scoliosis. Curves may progress rapidly during the adolescent growth spurt, and children need to be monitored every 3-6 months during this time with clinical assessment and spine radiographs if indicated. Typically, once the curve has progressed to Cobb angle of about 30 degrees, surgical intervention should be considered. Patients who are likely to require spine fusion at some point should be monitored with pulmonary function tests every six months. Decision-making for surgical management of scoliosis is closely related to pulmonary and cardiac function. An FVC below 30% may be a relative contraindication for spinal instrumentation for scoliosis because of increased perioperative mortality; however, with current improved pulmonary care this is not an absolute contraindication, and appropriate clinical judgment should prevail. Severe spinal deformity in DMD can lead to multiple problems, including poor sitting balance, difficulty with upright seating and positioning, pain, difficulty in parental or attendant care, and potential exacerbation of underlying restrictive respiratory compromise. Severe scoliosis and pelvic obliquity can, in some instances, completely preclude upright sitting in a wheelchair and decrease patient's quality of life. The main benefits of surgery are prevention of deformity and discomfort, rather than improvements in respiratory function. Spine surgery in DMD can enhance continued wheelchair mobility in later years and often improve quality of life.

**Anesthetic Issues**

Patients with DMD have an increased risk of complications when they undergo sedation or general anesthesia. The primary risks are determined by the degree of respiratory and cardiac impairments, but there are added risks of complications due to anesthesia. Patients with DMD are at increased risk for malignant hyperthermia and rhabdomyolysis when exposed to certain anesthetics, especially inhaled agents such as halothane, isoflurane, and sevoflurane. In addition, depolarizing muscle relaxant such as succinylcholine can increase the risk for development of rhabdomyolysis in DMD patients. Because of smooth muscle dysfunction, cardiac impairment, and decreased vascular control for bleeding, increased blood loss and hypotension can additionally complicate surgery. When undergoing surgery, patients with DMD should have a preoperative consultation with cardiac and pulmonary function tests, as well as anesthesiology consultation for pre-planned strategy for anesthesia (route and medications) with contingency preparations.

**Nutrition and Related Issues**

Obesity from reduced physical activity is a major concern in DMD, particularly at the onset of wheelchair dependence. Since many patients are now placed on corticosteroid treatment, weight gain is the most frequently reported side effect. At later stages of the disease (ages 17 to 21), significant weight loss becomes the predominant nutritional concern. This probably results from nutritional compromise along with increased protein and calorie requirements during the later stages of DMD, partially as a result of the increased work of breathing from restrictive lung disease. Osteoporosis is also a concern for the DMD population, and doubly important because of side effects from long-term corticosteroid treatment and frequent falls. Dual energy X-ray absorptiometry (DEXA) scan will inevitably show osteoporosis, and vitamin D + calcium supplements should be administered especially when being treated with corticosteroids. Constipation is another common problem in DMD and can be managed with a regular bowel program, adequate hydration, and laxatives.

**Dysphagia**

DMD patients have a high prevalence of dysphagia during the late stages of the disease. An assessment of the swallowing mechanism is best evaluated with a fluoroscopic video dynamic swallowing evaluation. DMD patients may also rarely develop acute gastric dilatation secondary to gastric paresis. Improved nourishment in DMD may lead to improved well-being and a better quality of life. Poor nutritional status, labored feeding/or symptoms of dysphagia are indications for initiation of supplemental enteral feedings via gastrostomy tube. Gastroesophageal reflux with risk of aspiration may be an indication for placement of a gastrojejunostomy tube.
Cognitive and Psychological Issues

Considering the presence of a dystrophin isoform in brain tissue, it is not surprising that DMD patients show mildly decreased intelligence quotient (IQ) scores compared with their peers and normative data. There may be a specific deficit with tasks requiring attention to complex verbal information, regardless of IQ. Mild impairments are noted on neuropsychological testing as well, without a specific area of strength or weakness. However, a suspected focal cognitive deficit warrants a thorough neurological evaluation to look for any other concomitant disease process. Identification of learning disability in a DMD patient necessitates an individual education plan with involvement of the school system and a school psychologist (and/or a speech-language pathologist). Also, addressing the emotional and psychological adaptation to a chronic and progressive illness is crucial to the care of DMD patients. Appropriate psychological support to the caregivers, parents, and the patients should be offered through the multidisciplinary clinic with the help of a psychologist and at times referral to a psychiatrist.

TREATMENT OPTIONS

Corticosteroids (prednisone, prednisolone, and deflazacort) are the primary medication treatments for DMD at this time. They have shown to increase muscle mass, increase strength, slow muscle deterioration, and prolong ambulation with essentially similar side effect profiles. With corticosteroids, muscle strength typically increased within 10 days, with maximal improvement noted at 3-6 months, maintained up to 24 months. However, the mechanism of action is still unclear. Recent studies suggest additional potential benefits of corticosteroids including amelioration of cardiac, pulmonary, and scoliosis complications in DMD. However, they do come with side effects that need to be closely monitored, so a thorough and balanced discussion regarding benefits and risks, both short- and long-term, should be had with the family prior to starting these agents. There are a number of consensus statements and reviews regarding the use of corticosteroids in DMD, and the reader is directed to these for further details.  

Briefly, the optimal regimen for prednisone/prednisolone is thought to be 0.75mg/kg/day. Alternatively, intermittent regimens such as 10 days on and 10 or 20 days off, and high dose (5 mg/kg/day) weekend pulses are available. Deflazacort is administered at 0.9mg/kg/day. At this time, there is little data regarding when to start and stop corticosteroid treatment. In general, it is common to start corticosteroids at the time of frequent falls or noticeable decline in muscle function with worsening gait (typically around 5 years), and stop at the time of transition to wheelchair. Some advocate earlier initiation of corticosteroids, but studies in very young children are lacking. Common side effects of corticosteroid use include: weight gain, Cushingoid appearance, behavior issues, skin problems, osteoporosis, vertebral fractures, growth suppression, insulin resistance, and cataract formation.

Research involving other pharmaco-agents and various strategies that can increase muscle bulk, improve strength, restore dystrophin expression, and upregulate utrophin (a protein homologue of dystrophin) in muscle membrane as well as research into stem cell and gene therapy are ongoing. Premature stop codon read-through medication such as Ataluren is applicable only to select DMD patients with a premature stop codon mutation. It is estimated that about 13-15% of DMD patients in the United States harbor such a premature nonsense mutation. These read-through agents have been shown to increase dystrophin expression in animal studies and are currently undergoing phase 2 clinical trials. Anti-sense oligonucleotide and exon skipping is a promising strategy for treatment of DMD that is more widely applicable. It utilizes small oligonucleotide molecules to change splicing around the region of the mutation to essentially skip the problematic exon and restore the reading frame. This strategy is applicable to a majority of DMD patients, since most of the disease-causing mutations are out-of-frame deletions and duplications. The restored reading frame then results in a dystrophin protein that is not full-length but that retains partial function, and therefore ameliorates the phenotype. A pilot clinical trial study has been started in Europe. Stem cell and gene therapy studies have shown promise in cell culture and animal studies, but still face many challenges including identification of optimal delivery methods, circumventing immunological problems, and cost effective and efficient production. Despite these challenges, stem cell and gene therapy studies are now beginning to make their way to clinical trials. Utrophin upregulation is an interesting idea that potentially can be applicable to all DMD patients; however, the research is in relatively early stages without any clinical trials at this time. Other pharmaco-agents such as creatine, glutamine, L-arginine, coenzyme Q10, idebenone, and pentoxifylline have shown some promise in previous studies; however, thus far have not been shown to impact function in a significant way.

Improving Functional Mobility

Generally, antigravity quadriceps are required for community ambulation. Some patients with more severe weakness may achieve short distance ambulation using KAFO bracing with or without a walker. Orthopedic surgical release of iliotibial band and heel cord contractures may allow the DMD patient to be braced in lightweight polypropylene KAFOs with the sole and ankle set at 90 degrees, drop-lock knee joints and an ischial weight-bearing polypropylene upper thigh component. At times, DMD patients who have followed excellent home stretching programs can be placed immediately into KAFO bracing without surgical tenotomies. However, one must exercise caution against aggressive orthopedic intervention and isolated heel cord tenotomies in DMD patients who are still ambulating independently. Overcorrection of the heel cord contracture in a DMD patient may result in immediate loss of the ability to walk without bracing unless the quadriceps are grade 4 or better. Disadvantages of braced ambulation center around the excessive energy cost of braced ambulation and safety concerns in the event of falls. DMD subjects with KAFO bracing will need gait training by physical therapy, and they need to be taught fall techniques as well as fall recovery. Weakness is the major cause of loss of ambulation in DMD, not contracture formation. Little evidence supports the efficacy of early prophylactic lower extremity surgery in DMD for independently producing prolonged ambulation. Resting night ankle splints are also provided to patients early in disease for prevention of ankle planter...
contractures and also for patient acceptance for its long-term use. As the disease progresses, it will be necessary for boys to utilize power mobility devices for functional mobility. Generally, children can be taught to safely operate a power wheelchair when they are at the developmental age of approximately two years. The power wheelchair prescription needs to consider that these boys will subsequently develop the need for a recline system, accommodate scoliosis and contractures, as well as a ventilator system. As the disease worsens, the power wheelchair electronics should be sufficiently flexible and sophisticated to incorporate alternative drive control systems, environmental control adaptations, and possibly communication systems in patients who are unable to vocalize.

REFERENCES


Supplement

The Effect of Exercise Training in Dystrophinopathies

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ABSTRACT

At this time, there is inadequate evidence from randomized controlled trials with sufficient sample size to make specific recommendations regarding the type, frequency, and intensity of exercise programs for individuals with dystrophinopathies. Nevertheless, there is a potential for aerobic training to improve the cardiopulmonary condition of individuals with dystrophinopathies, but the level and method of training depends on the type, stage, and severity of the disease. Results from aerobic studies performed almost uniformly show that individuals who are mildly affected by the dystrophinopathy or who are in the early stages of their disease demonstrate short-term cardiopulmonary improvements. In these individuals, aerobic exercise such as swimming, pool therapy, and recreation based exercises may reverse the effects of deconditioning and provide positive health benefits in terms of reduced adiposity, improved cardio respiratory status, improved sense of well being, and increased bone mass. Gentle submaximal strengthening exercises are recommended for ambulatory and early non ambulatory patients. Significant muscle pain, or myoglobinuria, is a sign of overexertion and should precipitate modification of the exercise or physical activity. More randomized controlled studies are needed to test the efficacy and safety of various training programs for short term and long term use.
The Effect of Exercise Training in Dystrophinopathies

AANEM Course

In able-bodied subjects, exercise increases muscle mass, muscle strength, cardiac function, pulmonary function, and fitness, which in turn, improves the individual's ability to perform activities of daily living and enhances independence. The lifting of weights during concentric (muscle shortens during contraction) or eccentric (muscle lengthens during contractions) exercise places stress on the muscle. This stress causes slight damage to the myofibers, which initiates transcriptional and splice mechanisms, protein turnover, and signaling pathways from hormone and cytokine receptors. This process involves a number of proteins that shuttle between sarcomeric and nonsarcomeric localizations and convey signals to the nucleus. Satellite cells, mononuclear, and myogenic progenitor cells that typically exist in a state of quiescence under the basal lamina are activated and fuse to the existing fiber, increasing the number of nuclei in the muscle while providing the machinery for additional contractile proteins. Exercise also decreases anxiety and depression, enhances feelings of well being, and increases vitality with age. Additionally, it plays a role in the primary and secondary development of chronic diseases. Exercise has been shown to reduce blood pressure, lower cholesterol, prevent obesity, and protect against the development of osteoporosis, heart disease, arthritis, and type 2 diabetes. Although preventing deconditioning, maintaining appropriate weight, and maintaining appropriate strength and endurance are major goals in managing NMDs, the role of strength training and aerobic exercise has not been established for individuals with DMD and BMD.

One of the major problems in establishing an exercise program in dystrophinopathies is the concern that exercise may cause overwork weakness in individuals with NMD. Over 50 years ago, Bennett and Knowlton raised concerns that overwork injury may occur as a result of exercise that equals or exceeds the maximum strength of the muscle in individuals with post polio. In 1971, Johnson and Braddock cited unsettling evidence regarding the use of exercise in individuals with all NMDs, regardless of the severity of the disease and the pathogenesis. As is true in most all effective therapies, exercise training has associated dose-dependent risks. Rhabdomyolysis, seen occasionally following intense physical activity, would be considered an overwork injury in healthy subjects. Numerous studies have shown that strength training can cause muscle damage in normal NM systems, especially eccentric contractions. In able-bodied subjects, these damaging effects can be ameliorated by proper training. However, it is not known whether progressive resistance training and aerobic exercise training is helpful for humans with dystrophinopathies who have sarcolemmal membranes that are susceptible to stress induced injuries.

Effect of Exercise in Humans With Dystrophinopathies

Very few randomized studies have systematically examined the effect of strengthening resistive exercise or aerobic exercise in persons with DMD and/or BMD. Most of the randomized controlled trials (RCT) have been small in size with inconsistent methodologies and results. Studies regarding the effect of exercise on the skeletal muscles of individuals with DMD have produced conflicting results. Some investigations have demonstrated that low intensity aerobic and resistance exercise maintains or even

disease is much more heterogeneous in BMD. In severely affected BMD patients, the average age of onset is 8 years, and most patients have difficulty climbing stairs by age 20. In the more common milder form, the average age of onset is 12 years, and patients have no problem climbing stairs at age 20. In these cases, death usually results from respiratory or cardiac failure between the fourth and seventh decade.

Two principal theories, neither of which is mutually exclusive, have been proposed to explain the pathogenesis of muscles from individuals with dystrophinopathies. Dystrophin deficiency destabilizes the dystrophin glycoprotein complex, impairing localization of the dystroglycan and sarcoglycans to the muscle membrane, and compromising the structural integrity of the sarcolemma membrane. Dystrophin is a high molecular weight cytoskeleton protein that is localized at the inner surface of the muscle membrane and is part of a dystrophin glycoprotein complex that also includes dystroglycan and sarcoglycans. This dystrophin glycoprotein complex provides a bridge across the muscle membrane; dystrophin couples F-actin in the cytoplasm with dystroglycan, which binds to merosin (laminin 2) in the extracellular matrix. Excessive mechanical stress creates micro and macro injuries to the sarcolemma membrane which causes excessive calcium ion influx, phospholipase activation, oxidative muscle injury, and ultimately, necrosis of the muscle fiber. As muscle damage progresses, connective tissue and fat replace the damaged muscle fibers. The second theory is that disruption of the dystrophin complex down regulates neuronal nitric oxide synthase (nNOS), which disrupts the exercise induced cell signaling pathway that regulates blood flow to the muscle and results in functional muscle ischemia. More recent studies have shown that when nNOS is not present at its normal location on the muscle membrane, the blood vessels that supply active muscles do not relax normally and show signs of fatigue. Thus, the pathophysiology of the disease may significantly affect its response to exercise. Exercise, particularly that which places a large amount of stress on the muscle fibers, such as high resistive and eccentric exercise, damages skeletal muscle in the dystrophinopathies. Even mild exercise has been implicated in causing functional muscle ischemia and fatigue in dystrophinopathy patients due to disruptions in nNOS signaling.

Although tremendous advances have been made in the past decade in an understanding of molecular genetic basis and pathophysiology of these dystrophinopathies, no effective treatment, with the possible exception of glucocorticosteroids in DMD, has been found for these patients. Thus, the primary rehabilitation goals are to maintain strength, endurance, function, independence, and quality of life. Clinicians have attempted to help alleviate weakness, atrophy, and fatigue through the use of physical interventions. Therapeutic modalities commonly used in physical medicine and rehabilitation include stretching, exercise, electrical stimulation, and heat with and without pharmacologic agents. These interventions are made at various points in the natural evolution of the disease to reduce pain, prevent, or reduce the development of contractures, increase strength, and maintain function for as long as possible. However, the potential benefits and risks of these interventions, particularly exercise regimens, have not been established in neuromuscular diseases (NMDs).
slightly improves strength in DMD patients. However, others have presented case study evidence that exercise induces weakness in dystrophinopathies. Garrod and associates noted that individuals with DMD increase their physical activity after steroid treatment, and suggest that this increased activity places their dystrophic deficient muscles under greater mechanical stress, predisposing them to muscle fiber damage and consequent myoglobinuria. A case study of a boy who had both spina bifida and BMD revealed that the dystrophic changes in the muscle biopsy were less severe in the LEs immobilized by spina bifida than the unaffected upper extremities. The authors suggested that this adds to the evidence that excessive exercise causes muscle damage in dystrophinopathies and should be restricted. Studies that have examined the effect of respiratory muscle training on patients with dystrophinopathies have also produced conflicting results, depending upon initial muscle strength. Several investigators have reported increased ventilatory strength and endurance following inspiratory and/or expiratory resistance training, while others have shown no changes. Koessler and associates demonstrated an improvement in maximum inspiratory pressure (MIP) and 12 s maximal voluntary ventilation after 24 months of inspiratory muscle training in 18 DMD patients and 9 spinal muscular atrophy patients whose FVC was greater than the predicted 25%. However, inspiratory muscles that were very weak or near their fatigue threshold showed no improvement after respiratory training. Sveen and associates studied the effect of endurance training (30 min of aerobic cycling, 3 to 4 times per week, at 65% of their maximum oxygen uptake(VO2) max for 12 weeks) in 11 ambulatory patients with mild BMD and seven matched, healthy subjects. They reported that aerobic endurance training increased VO2 max by 47%, maximal workload by 80%, and muscle strength by 13-40%, without causing muscle damage as indicated by muscle pathology and increased serum creatine kinase (CK). The results of these studies suggest that exercise studies are contraindicated on subjects with dystrophinopathies that have very weak muscles and are very susceptible to exercised induced damage. Further short-term and long-term studies regarding the effect of endurance exercise and mild resistance exercise are warranted for individuals who still have adequate strength, but require careful monitoring to prevent the occurrence of adverse effects from the exercise.

Effects of Exercise On Humans With Dystrophinopathies and Other Neuromuscular Diseases

The lack of good controlled studies in regards to the effects of exercise in these patients can be attributed to the rarity of dystrophinopathies. To obviate this difficulty, researchers frequently grouped subjects with dystrophinopathies with those who had other various NMDs, even though the severity, rate of progression, and disease type markedly affected the exercise response. However, this action creates several problems because there is no reason to believe that diseases affecting the anterior horn cells, peripheral nerves, and/or muscles would respond similarly to exercise training. Despite these limitations, these studies did demonstrate that individuals with NMDs experienced some beneficial responses to exercise training. In slowly progressive or static NMDs, the goal of resistance exercise is to increase strength, thereby giving the patient increased capacity to perform daily functions. A number of investigations combin-
only a minor increase in apoptotic cells was detectable. This provided the initial evidence that exercise may trigger apoptosis in dystrophin deficient mice. Using fluorescent dye, Clarke and associates examined the triceps muscles of mdx mice after a single bout of downhill running. Seventy-five percent of the fibers of the mdx triceps exhibited transient membrane disruptions, which was seven fold greater than the number of control mice. Furthermore, no difference was observed between muscles of control mice following running and those of non exercised control mice. Brusee examined the effect of downhill running for 3 days on the histology of mdx mice. He reported a 31% increase in positive staining for Evans blue muscle in young mdx mice, while there was only a 0-3% increase in staining in normal muscle. Stained fibers were also present in 2-15 % of nonexercised mdx mice. Further evidence of injury and repair was shown by Vilquin, who investigated skeletal muscle fibers in transgenic dystrophinless mice expressing beta galactosidase. Adult mdx/beta galactosidase (dystrophin negative) and normal/beta galactosidase (dystrophin positive) mice were submitted to one short session of eccentric, downhill running exercise. All of the running experiments revealed an increased susceptibility to injury in dystrophic animals as compared to controls. However, there are not enough reports that examine the effect of highly resistive strength training exercises in dystrophic animals to allow any conclusions to be drawn.

Nearly all animal investigations reported a relatively normal and beneficial adaptation to aerobic exercise. Whether by running, swimming, or with the use of electrical stimulation, the benefits of high repetitive, low impact training typically has a greater effect on the more oxidative fibers and may reduce the risk for further mechanical damage to these oxidative fibers. However, it has little impact on fast twitch fibers. The major factors determining the beneficial or deleterious effect of exercise training in animals with muscular dystrophy are: (1) the age of the animal at the start of the study; (2) the severity of the dystrophy at the start of the study; (3) the intensity of the training (submaximal or maximal); (4) the length of the training; and (5) the type of training (repetitive aerobic or resistive strength). These factors are similar to those reported in humans with dystrophy. The beneficial adaptations to mild aerobic exercise training included an increase in muscle strength and a reduction in muscle degeneration. There was a hypertrophic response in the muscles that were not severely affected by the dystrophy. High repetitive, low impact exercise increased the oxidative capacity and the proportion of oxidative fibers, especially in slow twitch muscles. Younger animals tended to benefit more from exercise studies than older animals. However, high repetitive exercise typically had no effect, or had a deleterious effect in fast twitch muscles that were more severely affected by the disease and remain more likely to incur damage by eccentric exercise.

Recommendations

Recently, the Centers for Disease Control gathered 84 experts and applied the RAND/UCLA Appropriateness Method (RAM) to develop care recommendations and interventions for individuals with DMD and BMD. Instead of using consensus driven methods, the RAM combines scientific evidence with the collective judgment of experts to yield a statement regarding the appropriateness of clinical interventions. This methodology also identifies areas where there is disagreement and uncertainty among the experts. Using the RAM, the group determined that limited research has been conducted out concerning the type, frequency, and intensity of exercise that is optimal in BMD and DMD. Therefore, many of the recommendations were based upon the known pathophysiology of the disease and from animal studies. Nevertheless, the group was able to make the following recommendations:

- High-resistance strength training and eccentric exercise is inappropriate in DMD across the lifespan due to concerns regarding contraction induced muscle fiber injury.
- To avoid disuse atrophy and other secondary complications noted with sedentary existence, it is necessary that all ambulatory patients or those in the early nonambulatory stage participate in regular submaximal (gentle) strengthening, including a combination of pool exercises and recreation based exercises in the community.
- Swimming, which may have benefits for aerobic conditioning and respiratory exercise, is highly recommended from the early ambulatory to early non ambulatory phases.
- Additional benefits may be provided by low resistance strength training and optimization of upper body function.
- Significant muscle pain or myoglobinuria in the 24-hour period following a specific activity is a sign of overexertion and contraction induced injury, and the activity should be modified.

CONCLUSIONS

Currently, there is a lack of adequate evidence from randomized controlled trials with sufficient sample size to provide specific recommendations regarding the type, frequency, and intensity of exercise programs for individuals with dystrophinopathies. More randomized controlled studies will be needed to test the efficacy and safety of various training programs for short term and long term use.

REFERENCES


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