Myopathies
Issues in Diagnosis and Treatment

Crossfires
Piriformis Syndrome, Thoracic Outlet Syndrome, and TT Syndrome

Photo by Michael D. Stubblefield, MD
Myopathies: Issues in Diagnosis and Treatment

Anthony A. Amato, MD
Richard J. Barohn, MD
Andrew L. Mammen, MD, PhD
Matthew P. Wicklund, MD
Please be aware that some of the medical devices or pharmaceuticals discussed in this handout may not be cleared by the FDA or cleared by the FDA for the specific use described by the authors and are “off-label” (i.e., a use not described on the product’s label). “Off-label” devices or pharmaceuticals may be used if, in the judgment of the treating physician, such use is medically indicated to treat a patient’s condition. Information regarding the FDA clearance status of a particular device or pharmaceutical may be obtained by reading the product’s package labeling, by contacting a sales representative or legal counsel of the manufacturer of the device or pharmaceutical, or by contacting the FDA at 1-800-638-2041.
# Myopathies: Issues in Diagnosis and Treatment

## Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Course Objectives &amp; Course Committee</td>
<td>4</td>
</tr>
<tr>
<td>Faculty</td>
<td>5</td>
</tr>
<tr>
<td>Clinical Approach to Muscle Disease</td>
<td>7</td>
</tr>
<tr>
<td><em>Richard J. Barohn, MD</em></td>
<td></td>
</tr>
<tr>
<td>The Autoimmune Myopathies: Diagnosis and Treatment</td>
<td>19</td>
</tr>
<tr>
<td><em>Andrew L. Mammen, MD, PhD</em></td>
<td></td>
</tr>
<tr>
<td>The Limb-Girdle Muscular Dystrophies</td>
<td>25</td>
</tr>
<tr>
<td><em>Matthew P. Wicklund, MD</em></td>
<td></td>
</tr>
<tr>
<td>Myopathy Potpourri</td>
<td>33</td>
</tr>
<tr>
<td><em>Anthony A. Amato, MD</em></td>
<td></td>
</tr>
<tr>
<td>CME Questions</td>
<td>39</td>
</tr>
</tbody>
</table>

---

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

**Course Chair:** Anthony A. Amato, MD

The ideas and opinions expressed in this publication are solely those of the specific authors and do not necessarily represent those of the AANEM.
Objectives

Objectives - Participants will acquire skills to (1) narrow the differential diagnosis of patients presenting to them for evaluation of weakness; (2) order more appropriate tests to come up with the accurate diagnosis; and (3) better evaluate and treat patients with possible inflammatory myopathy or muscular dystrophy.

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

Physicians who are eligible to attend the AANEM meeting are MDs, DOs, and overseas equivalents.

Healthcare Professionals and Researchers who are not AANEM members must receive a letter of support from a Fellow AANEM member to attend the meeting.

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 live activity for a maximum of 3.25 AMA PRA Category 1 Credits™. If purchased, the AANEM designates this enduring material for a maximum of #.## AMA PRA Category 1 Credits™. 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. Physicians should claim only the credit commensurate with the extent of their participation in the activity. CME for this course is available 09/2011 - 09/2014.

CEUs Credit - The AANEM has designated this live activity for a maximum of 3.25 AANEM CEUs. If purchased, the AANEM designates this enduring material for a maximum of #.## CEUs.

2010-2011 Course Committee

Shawn J. Bird, MD, Chair
Philadelphia, PA

Taylor B. Harrison, MD
Atlanta, GA

A. Arturo Leis, MD
Jackson, MS

Gary L. Branch, DO
Owosso, MI

Laurence J. Kinsella, MD
Saint Louis, MO

Marcy C. Schlinger, DO
Okemos, MI

Lawrence W. Frank, MD
Elmhurst, IL

Shashi B. Kumar, MD
Tacoma, WA

Benjamin S. Warfel, MD
Lancaster, PA

2010-2011 AANEM President

Timothy R. Dillingham, MD, MS
Milwaukee, Wisconsin
Myopathies: Issues in Diagnosis and Treatment

Faculty

Anthony A. Amato, MD
Vice-chairman, Department of Neurology
Director, Neuromuscular Division and Clinical Neurophysiology Laboratory
Brigham and Women’s Hospital
Professor of Neurology
Harvard Medical School
Boston, Massachusetts

Dr. Amato is the vice-chairman of the department of neurology and the director of the neuromuscular division and clinical neurophysiology laboratory at Brigham and Women’s Hospital in Boston. He is also professor of neurology at Harvard Medical School. He is the director of the Partners Neuromuscular Medicine fellowship program. Dr. Amato is an author or coauthor on over 150 published articles, chapters, and books. He cowrote the textbook Neuromuscular Disorders with Dr. James Russell. He has been involved in clinical research trials involving patients with amyotrophic lateral sclerosis, peripheral neuropathies, neuromuscular junction disorders, and myopathies.

Richard J. Barohn, MD
Chair of the Department of Neurology
University of Kansas Medical Center
Kansas City, Kansas

Dr. Richard Barohn is chair of the Department of Neurology at the University of Kansas Medical Center (KUMC) and has joint appointments in the departments of Pathology, Hearing and Speech, and Physiology. He is a graduate of the 6-year BA/MD program at the University of Missouri-Kansas City School of Medicine. He completed a neurology residency at Wilford Hall United States Air Force Medical Center and completed a neuromuscular fellowship at Ohio State University. He served on the faculty at the University of Texas Health Science Center in San Antonio, Texas from 1989 to 1993. He then joined the faculty at the University of Texas Southwestern Medical Center in Dallas in 1993. In 2001, he assumed his current role at KUMC and was the neurology residency training director from 2001 to 2003. Prior to joining KUMC, he developed and directed the clinical neurophysiology training program at the University of Texas Southwestern. Dr. Barohn is the author of more than 160 journal publications, 260 abstracts, and 40 book chapters on various aspects of neuromuscular disease. He recently completed terms on the editorial boards for Neurology and Muscle and Nerve, and currently serves as associate editor for the Journal of Clinical Neuromuscular Disorders. He was the founding chair of the Section of Neuromuscular Disease in the American Academy of Neurology. He is on the national medical advisory boards for the Myasthenia Gravis Foundation of America, the Guillain-Barré Syndrome Foundation International, and The Myositis Association. He also serves on the executive committee of the national ALS Research Group. He was the recipient of the Alumni Achievement Award for Medicine from the University of Missouri-Kansas City, and Faculty Investigator Research Award at KUMC.

Andrew L. Mammen, MD, PhD
Co-Director, Johns Hopkins Myositis Center
Assistant Professor
Departments of Neurology and Medicine
The Johns Hopkins Bayview Medical Center
Baltimore, Maryland

Dr. Mammen is codirector of the Johns Hopkins Myositis Center in Baltimore, Maryland. He is also assistant professor of neurology and medicine at the Johns Hopkins University School of Medicine. Dr. Mammen’s research focuses on elucidating the mechanisms underlying the initiation and maintenance of autoimmune muscle disease. He and his colleagues recently discovered that patients with statin-associated autoimmune myopathy make antibodies against HMG-CoA reductase, the pharmacological target of statins.
Matthew P. Wicklund, MD
Professor
Department of Neurology
Milton S. Hershey Medical Center
Pennsylvania State University School of Medicine
Hershey, Pennsylvania

Dr. Wicklund recently transitioned to the Pennsylvania State University School of Medicine in Hershey, Pennsylvania, as professor of neurology. After serving in roles as program director, chairman, and consultant to the surgeon general, he retired from the United States Air Force in 2010. Dr. Wicklund is an author or coauthor of 30 published articles, chapters, and abstracts and has lectured at national meetings for more than a decade. He has been involved in clinical care and research trials involving patients with amyotrophic lateral sclerosis, peripheral neuropathies, neuromuscular junction disorders, and myopathies.
Myopathies are disorders in which there is a primary functional or structural impairment of skeletal muscle. Myopathies can be distinguished from other disorders of the motor unit, including motor neuron disorders, peripheral neuropathies, and neuromuscular junction diseases, by characteristic clinical and laboratory features. The first goal in approaching a patient with a suspected muscle disease is to determine the correct site of the lesion. Once localized to the muscle, the next step is to identify whether the myopathy is due to a defect in the muscle channel, muscle structure, or a dysfunction in muscle metabolism. The second goal is to determine the cause of the myopathy. In general, myopathies can be classified into hereditary and acquired disorders (see Table 1). The third and final goal is to determine if there is a specific treatment and, if not, to optimally manage the patient’s symptoms in order to maximize their functional abilities and enhance their quality of life.

**CLINICAL EVALUATION**

The most important element of evaluating a patient with a suspected myopathy is obtaining a thorough history. The history should allow the physician to make a reasonable preliminary diagnosis that places the patient into one of the categories in Table 1. The findings on the physical examination, and in particular the distribution of muscle weakness, should provide additional information in determining the correct diagnosis. The results of the laboratory studies (blood tests, electromyography [EMG], muscle biopsy, molecular genetic studies) then play a confirmatory diagnostic role.

The first step is to ask six key questions based on the patient’s symptoms and signs.

1. **Which “Negative” and/or “Positive” Symptoms and Signs Does the Patient Demonstrate?**

   Symptoms and signs of muscle disease (see Table 2) can be divided into “negative” complaints such as weakness, exercise intolerance, fatigue, and muscle atrophy and “positive” complaints such as myalgias, cramps, contractures, myoglobinuria, and muscle stiffness.

   Weakness is by far the most common “negative” symptom reported by a patient with muscle disease. If the weakness involves the lower
Fatigue is a much less useful “negative” symptom since it is nonspecific and may reflect a patient’s cardiopulmonary status, level of conditioning, overall health, sleeping habits, or emotional state. Many patients who complain of diffuse global “weakness” or fatigue do not have a disorder of muscle, particularly if the neurologic examination is normal. On the other hand, abnormal fatigability after exercise can result from certain metabolic and mitochondrial myopathies, and it is important to define the duration and intensity of exercise that provokes the fatigue.

“Positive” symptoms associated with myopathies may include myalgias, cramps, contractures, myotonia, or myoglobinuria. Myalgia, like fatigue, is another nonspecific symptom of some myopathies (see Table 3). Myalgias may be episodic (metabolic myopathies) or nearly constant (inflammatory muscle disorders). However, muscle pain is usually not common in most muscle diseases, and pain is more likely to be due to orthopedic or rheumatologic disorders. It is rare for a muscle disease to be responsible for vague aches and muscle discomfort in the presence of a normal neuromuscular examination and laboratory studies.

A specific type of muscle pain is the involuntary muscle cramp. Cramps may last from seconds to minutes and are usually localized to a particular muscle region. They are typically benign, occurring frequently in normal individuals, and are seldom a feature of a primary myopathy. Cramps are characterized by rapidly firing motor unit discharges on needle EMG. Cramps can occur with dehydration, hyponatremia, azotemia, and myxedema. They also can occur in disorders of the nerve or motor neuron (especially amyotrophic lateral sclerosis [ALS]).

Muscle contractures are uncommon but can superficially resemble a cramp. They are typically provoked by exercise in patients with glycolytic enzyme defects. Contractures differ from cramps in that they usually last longer and are electrically silent with needle EMG. Muscle contractures should not be confused with fixed tendon contractures.

Myotonia is the phenomena of impaired relaxation of muscle after forceful voluntary contraction and most commonly involves the hands and eyelids. Myotonia is due to repetitive depolarization of the muscle membrane. Patients may complain of muscle stiffness or tightness resulting in difficulty releasing their handgrip after a handshake, unscrewing a bottle top, or opening their eyelids if they forcefully shut their eyes. Myotonia classically improves with repeated exercise. In contrast, patients with paramyotonia congenita demonstrate “paradoxical myotonia,” in that symptoms are typically worsened by exercise or repeated muscle contractions. Exposure to cold results in worsening of both myotonia and paramyotonia. The muscle disorders associated with muscle stiffness are listed in Table 4.

Myoglobinuria is a relatively uncommon manifestation of muscle disease and is caused by the excessive release of myoglobin from muscle during periods of rapid muscle destruction (rhabdomyolysis). Severe myoglobinuria can result in renal failure due to acute tubular necrosis. If a patient complains of exercise-induced weakness and myalgias, they should be asked if their urine has ever turned coke-colored or red during or after these episodes.

Table 2: Symptoms and signs associated with myopathies

<table>
<thead>
<tr>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness</td>
<td>Myalgias</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Cramps</td>
</tr>
<tr>
<td>Exercise intolerance</td>
<td>Contractures</td>
</tr>
<tr>
<td>Muscle atrophy</td>
<td>Stiffness/ inability to relax</td>
</tr>
<tr>
<td></td>
<td>Myoglobinuria</td>
</tr>
<tr>
<td></td>
<td>Hypertrophy</td>
</tr>
</tbody>
</table>

Table 3: Muscle disorders associated with myalgias

<table>
<thead>
<tr>
<th>Mitochondrial myopathies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory myopathies (polymyositis, dermatomyositis)</td>
</tr>
<tr>
<td>Infectious myositis (especially viral)</td>
</tr>
<tr>
<td>Drug-induced myopathies (lovastatin, chloroquine)</td>
</tr>
<tr>
<td>Hypothyroid myopathy</td>
</tr>
<tr>
<td>Myoadenylate deaminase deficiency</td>
</tr>
<tr>
<td>Tubular aggregate myopathy</td>
</tr>
<tr>
<td>X-linked myalgia and cramps (Becker muscular dystrophy variant)</td>
</tr>
<tr>
<td>Eosinophilia-myalgia syndrome</td>
</tr>
</tbody>
</table>

Table 4: Myopathies associated with muscle stiffness

<table>
<thead>
<tr>
<th>Myotonic dystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myotonia congenital</td>
</tr>
<tr>
<td>Paramyotonia congenital</td>
</tr>
<tr>
<td>Proximal myotonic myopathy</td>
</tr>
<tr>
<td>Hyperkalemic periodic paralysis</td>
</tr>
<tr>
<td>Hypothyroid myopathy</td>
</tr>
</tbody>
</table>

extremities, patients will complain of difficulty climbing stairs, arising from a low chair or toilet, or getting up from a squatted position. When the upper extremities are involved, patients notice trouble lifting objects over their head and brushing their hair. These symptoms in the arms and legs indicate proximal muscle weakness, which is probably the most common site of weakness in a myopathic disorder (see below). Less commonly, patients with myopathies can complain of distal weakness manifested as difficulty opening jars, inability to turn a key in the ignition, or tripping due to foot drop. Some myopathies may also result in cranial muscle weakness resulting in complaints of dysarthria, dysphagia, or ptosis.
Recurrent myoglobinuria is usually due to an underlying metabolic myopathy (see Table 5), whereas isolated episodes, particularly occurring after unaccustomed strenuous exercise, are frequently idiopathic.

2. What Is the Temporal Evolution?

It is obviously important to determine the onset, duration, and evolution of the patient’s symptoms and signs of muscle disease. Did the weakness (or other symptoms) first manifest at birth or was the onset in the first, second, third, or later decade (see Table 6)? Identifying the age that symptoms began can provide crucial information leading to the correct diagnosis. For example, symptoms of Duchenne muscular dystrophy (DMD) usually are identified by age 3, whereas most facioscapulohumeral muscular dystrophies (FSHDs) and limb-girdle muscular dystrophies (LGMDs) begin in adolescence or later. Of the inflammatory myopathies, dermatomyositis occurs in children and adults, polymyositis rarely occurs in children but at any decade in the adult years, and inclusion body myositis (IBM) occurs most commonly in the elderly.

It is also imperative to determine the evolution and duration of the disease. Myopathies can present with either constant weakness (muscular dystrophies, inflammatory myopathies) or episodic periods of weakness with normal strength interictally (periodic paralysis, metabolic myopathies due to certain glycolytic pathway disorders). The episodic disorders have acute weakness that can return to normal strength within hours or days. The tempo of the disorders with constant weakness can vary from: 1) acute or subacute progression in some inflammatory myopathies (dermatomyositis and polymyositis), 2) chronic slow progression over years (most muscular dystrophies), or 3) nonprogressive weakness with little change over decades (congenital myopathies). Finally, both constant and episodic myopathic disorders can have symptoms that may be monophasic or relapsing. For example, polymyositis can occasionally have an acute monophasic course with complete resolution of strength within weeks or months.

Table 5 Causes of myoglobinuria

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged, intensive exercise</td>
</tr>
<tr>
<td>Viral and bacterial infections</td>
</tr>
<tr>
<td>Drugs and toxins (especially alcohol)</td>
</tr>
<tr>
<td>Neuroleptic malignant syndrome</td>
</tr>
<tr>
<td>Heat stroke</td>
</tr>
<tr>
<td>Trauma (crush injuries)</td>
</tr>
<tr>
<td>Severe metabolic disturbances, including prolonged fever</td>
</tr>
<tr>
<td>Inflammatory myopathies (rare)</td>
</tr>
<tr>
<td>Limb Girdle MD 2C-F (sarcoglycanopathies)</td>
</tr>
<tr>
<td>Metabolic myopathies</td>
</tr>
<tr>
<td>Glycogenoses (myophosphorylase deficiency)</td>
</tr>
<tr>
<td>Lipid disorders (carnitine palmitoyltransferase deficiency)</td>
</tr>
<tr>
<td>Malignant hyperthermia (Central core myopathy, Duchenne MD)</td>
</tr>
</tbody>
</table>

Table 6 Diagnosis of myopathy based on age of onset

<table>
<thead>
<tr>
<th>Myopathies presenting at birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital myotonic dystrophy</td>
</tr>
<tr>
<td>Centronuclear (myotubular) myopathy</td>
</tr>
<tr>
<td>Congenital fiber-type disproportion</td>
</tr>
<tr>
<td>Central core disease</td>
</tr>
<tr>
<td>Nemaline (rod) myopathy</td>
</tr>
<tr>
<td>Congenital muscular dystrophy</td>
</tr>
<tr>
<td>Lipid storage diseases (carnitine deficiency)</td>
</tr>
<tr>
<td>Glycogen storage diseases (acid maltase deficiency)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Myopathies presenting in childhood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscular dystrophies—Duchenne, Becker, Emery-Dreifuss, facioscapulohumeral, limb-girdle, Congenital</td>
</tr>
<tr>
<td>Inflammatory myopathies—dermatomyositis, polymyositis (rarely)</td>
</tr>
<tr>
<td>Congenital myopathies—nemaline myopathy, centronuclear myopathy, central core</td>
</tr>
<tr>
<td>Lipid storage disease (carnitine deficiency)</td>
</tr>
<tr>
<td>Glycogen storage disease (acid maltase deficiency)</td>
</tr>
<tr>
<td>Mitochondrial myopathies</td>
</tr>
<tr>
<td>Endocrine-metabolic disorders—hypokalemia, hypocalcemia, hypercalcemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Myopathies presenting in adulthood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscular dystrophies—limb-girdle, facioscapulohumeral, Becker, Emery-Dreifuss</td>
</tr>
<tr>
<td>Inflammatory myopathies—polymyositis, dermatomyositis, inclusion body myositis, viral (HIV)</td>
</tr>
<tr>
<td>Metabolic myopathies—acid maltase deficiency, lipid storage diseases, debrancher deficiency, phosphorlase b kinase deficiency</td>
</tr>
<tr>
<td>Mitochondrial myopathies</td>
</tr>
<tr>
<td>Endocrine myopathies—thyroid, parathyroid, adrenal, pituitary disorders</td>
</tr>
<tr>
<td>Toxic myopathies—alcohol, corticosteroids, local injections of narcotics, colchicine, chloroquine</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
</tr>
<tr>
<td>Distal myopathies</td>
</tr>
<tr>
<td>Nemaline myopathy</td>
</tr>
<tr>
<td>Centronuclear myopathy</td>
</tr>
</tbody>
</table>

HIV = human immunodeficiency virus

Patients with periodic paralysis or metabolic myopathies can have recurrent attacks of weakness over many years, while a patient with acute rhabdomyolysis due to cocaine may have a single episode.

3. Is There a Family History of a Myopathic Disorder?

Since many myopathies are inherited, obtaining a thorough family history is obviously of great importance in making a correct diagnosis. A detailed family tree should be completed to look
for evidence of autosomal dominant, autosomal recessive, and X-linked patterns of transmission. Questions regarding family members’ use of canes or wheelchairs, skeletal deformities, or functional limitations are usually more informative than vague questions such as, “Does any member of your family have a muscle disease?” Identifying a particular hereditary pattern can not only help in correctly diagnosing the specific myopathy (see Table 7), but is also of tremendous importance in providing appropriate genetic counseling.

4. Are There Precipitating Factors that Trigger Episodic Weakness or Myotonia?

A history of precipitating factors that might trigger or exacerbate symptoms of weakness or myotonia should be explored. It is important to ask the patient if there is any history of either illegal drug use or prescription medication use that might produce a myopathy. Drugs that can cause toxic myopathies are listed in Table 8. A history of weakness, pain, and/or myoglobinuria which is provoked by exercise might suggest the possibility of a glycolytic pathway defect. Episodes of weakness that occur in association with a fever would be supportive of a diagnosis of carnitine palmityl transferase deficiency. Periodic paralysis is characteristically provoked by exercise and ingestion of a carbohydrate meal followed by a period of rest. Patients with paramyotonia congenita frequently report that cold exposure may precipitate their symptoms of muscle stiffness.

5. Are There Associated Systemic Symptoms or Signs?

Involvement of organs or tissues other than muscle may also provide helpful clues in making the appropriate diagnosis. Cardiac disease (see Table 9) may be associated with myotonic dystrophy, DMD or Becker muscular dystrophy (BMD), LGMD 1B (laminopathy), LGMD 2I (fukutin-related protein), LGMD 2C-F (sarcoglycanopathies), LGMD 2G (telethoninopathies), Emery-Dreifuss muscular dystrophy (EDMD), and Andersen’s syndrome.

Respiratory failure may be the presenting symptom of myotonic dystrophy, centronuclear myopathy, nemaline myopathy, or acid maltase deficiency (see Table 10). Eventually, many myopathies will affect respiratory muscle strength, highlighting the need for consistent monitoring of pulmonary function studies throughout the disease course. Once symptoms of hypoventilation are evident, supportive care with noninvasive positive pressure ventilation and assistive devices for clearance of upper airway secretions should be employed.

Hepatomegaly may be seen in myopathies associated with deficiencies in acid maltase, debranching enzyme, and carnitine. The presence of cataracts, frontal balding, and mental retardation strongly suggests the diagnosis of myotonic dystrophy. Dysmorphic features may be associated with the congenital myopathies. The presence of a rash is extremely helpful in confirming the diagnosis of dermatomyositis. Musculoskeletal contractures can occur in many myopathies of a longstanding duration. However, contractures developing early in the course of the disease, especially at the elbows, can be a clue to EDMD, LGMD 1B (laminopathy), and Bethlem myopathy. Evidence of
diffuse systemic disease can indicate amyloidosis, sarcoidosis, endocrinopathy, collagen-vascular disease, infectious disease, or a mitochondrial disorder.

6. What Is the Distribution of Weakness?

In order to determine the distribution of muscle weakness, it is important to know which muscles to test and how to grade their power. Muscle strength can be tested by manual testing and from observation of functional activity (see Table 11). Functional testing is particularly informative in young children who usually cannot cooperate with formal manual muscle testing and in adults with “give-way” weakness who present with complaints of muscle pain.

In performing manual muscle testing of the upper extremities, it is necessary to assess shoulder abduction, external, and internal rotation; elbow flexion and extension; wrist flexion and extension; and finger and thumb extension, flexion, and abduction. Muscle groups that should be tested in the lower extremities include hip flexion, extension, and abduction; knee flexion and extension; ankle dorsiflexion, planar flexion, inversion, and eversion; and toe extension and flexion. All muscle groups should be tested bilaterally and preferably against gravity. Neck flexors should be assessed in the supine position and neck extensors in the prone position. Knee extension and hip flexion should be tested in the seated position, knee flexion should be tested prone, and hip abduction should be tested in the lateral decubitus position. If testing against gravity is
not performed, the presence of significant muscle weakness can escape recognition.

Assessment of muscle strength is usually based on the expanded MRC (Medical Research Council of Great Britain) grading scale of 0 to 5 (see Table 12).

Finally, cranial nerve muscles such as the orbicularis oculi and oris, extraocular muscles, tongue, and palate should be examined. These may be best tested by observation of functional activities such as asking the patient to whistle, suck from a straw, and smile.

In addition to manual muscle testing and functional testing, muscles should be inspected for evidence of atrophy or hypertrophy. Atrophy of proximal limb muscles is common in most chronic myopathies. However, certain myopathies may demonstrate atrophy in specific groups that correspond to severe weakness in those muscles and provide additional diagnostic clues. For example, atrophy of the periscapular muscles associated with scapular winging is characteristic of FSHD. Scapular winging is also seen in patients with LGMD 1B (laminopathy), LGMD 2A (calpainopathy), and LGMD 2C-F (sarcoglycanopathies). Selective atrophy of the quadriceps muscles and forearm flexor muscles is highly suggestive of IBM. Distal myopathies may have profound atrophy of the anterior or posterior lower extremity compartments. On the other hand, muscles can show evidence of hypertrophy in some myotonic conditions such as myotonia congenita. Muscle hypertrophy is also characterized by disorders including amyloidosis, sarcoidosis, and hypothyroid myopathy. In DMD and BMD, the calf muscles demonstrate “pseudohypertrophy” due to replacement with connective tissue and fat. Calf muscle hypertrophy is also characteristically seen in LGMD 2G (telethoninopathy), 50% of the patients will show calf hypertrophy and 50% will demonstrate calf atrophy. Focal muscle enlargement can also be due to a neoplastic or inflammatory process, ectopic ossification, tendon rupture, or partial denervation.

**PATTERN RECOGNITION APPROACH TO MYOPATHIC DISORDERS**

After answering the six key questions obtained from the history and neurologic examination outlined above, the physician can attempt to classify a myopathic disorder into one of six distinctive patterns of muscle weakness, each with a limited differential diagnosis. The final diagnosis can then be confirmed based on information from a selective number of laboratory studies.

**Pattern 1: Proximal Limb-girdle Weakness**

The most common pattern of muscle weakness in myopathies is symmetric weakness affecting predominantly the proximal muscles of the legs and arms or the so-called “limb-girdle” distribution. The distal muscles are usually involved, but to a much lesser extent. Neck extensor and flexor muscles are also frequently affected. This pattern of weakness is seen in most hereditary and acquired myopathies and, therefore, is the least specific in arriving at a particular diagnosis.
**Pattern 2: Distal Weakness**

Distal weakness predominantly involves the distal muscles of the upper or lower extremities (anterior or posterior compartment muscle groups) (see Table 13). Depending on the diagnosis and severity of disease, proximal muscles may also be affected. The involvement is usually, although not invariably, symmetric. Selective weakness and atrophy in distal extremity muscles is more commonly a feature of neuropathies and, therefore, a careful sensory and reflex examination must always be performed in patients presenting with this phenotype.

**Pattern 3: Proximal Arm/Distal Leg Weakness (Scapuloperoneal)**

Proximal arm/distal leg weakness affects the periscapular muscles of the proximal arm and the anterior compartment muscles of the distal lower extremity, or the so-called “scapuloperoneal” distribution (see Table 13). The scapular muscle weakness is usually characterized by scapular winging. Weakness can be very asymmetric. When this pattern is associated with facial weakness, it is highly suggestive of a diagnosis of FSHD. Other hereditary myopathies that are associated with a scapuloperoneal distribution of weakness include scapuloperoneal dystrophy, EDMD, LGMD 1B (laminopathies), LGMD 2A (calpain), LGMD 2C-F (sarcoglycans), congenital myopathies, and acid maltase deficiency.

**Pattern 4: Distal Arm/Proximal Leg Weakness**

Distal arm/proximal leg weakness is associated with distal arm weakness involving the distal forearm muscles (wrist and finger flexors) and proximal leg weakness involving the knee extensors (quadriceps). The facial muscles are usually spared. Involvement of other muscles is extremely variable. In addition, the weakness is often asymmetric between the two sides, which is uncommon in most myopathies. This pattern is essentially pathognomonic for IBM. This pattern may also represent an uncommon presentation of myotonic dystrophy. However, unlike IBM, muscle weakness is symmetric.

**Pattern 5: Ptosis with or without Ophthalmoplegia**

Myopathies presenting with predominant involvement of ocular and/or pharyngeal muscles represent a relatively limited group of disorders (see Table 14). The eye involvement principally results in ptosis and ophthalmoplegia which usually, although not always, occurs without symptoms of diplopia. Facial weakness is not uncommon and extremity weakness is extremely variable, depending on the diagnosis.

The combination of ptosis, ophthalmoplegia without diplopia, and dysphagia should suggest the diagnosis of oculopharyngeal dystrophy, especially if the onset is in middle-age or later. Ptosis and ophthalmoplegia without prominent pharyngeal involvement is a hallmark of many of the mitochondrial myopathies. Ptosis and facial weakness without ophthalmoplegia is a common feature of myotonic dystrophy and FSHD.
Table 18 Channelopathies And Related Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical features</th>
<th>Pattern of inheritance</th>
<th>Chromosome</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloride channelopathies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myotonia congenita</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thomsen’s disease</td>
<td>Myotonia</td>
<td>AD</td>
<td>7q35</td>
<td>CLC-1</td>
</tr>
<tr>
<td>Becker type</td>
<td>Myotonia and weakness</td>
<td>AR</td>
<td>7q35</td>
<td>CLC-1</td>
</tr>
<tr>
<td>Sodium channelopathies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paramyotonia congenita</td>
<td>Paramyotonia</td>
<td>AD</td>
<td>17q13.1-13.3</td>
<td>SCNA4A</td>
</tr>
<tr>
<td>Hyperkalemic periodic paralysis</td>
<td>Periodic paralysis and myotonia and paramyotonia</td>
<td>AD</td>
<td>17q13.1-13.3</td>
<td>SCNA4A</td>
</tr>
<tr>
<td>Potassium-aggravated myotonias</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myotonia fluctuans</td>
<td>Myotonia</td>
<td>AD</td>
<td>17q13.1-13.3</td>
<td>SCNA4A</td>
</tr>
<tr>
<td>Myotonia permanens</td>
<td>Myotonia</td>
<td>AD</td>
<td>17q13.1-13.3</td>
<td>SCNA4A</td>
</tr>
<tr>
<td>Acetazolamide-responsive myotonia</td>
<td>Myotonia</td>
<td>AD</td>
<td>17q13.1-13.3</td>
<td>SCNA4A</td>
</tr>
<tr>
<td>Calcium channelopathies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemic periodic paralysis</td>
<td>Periodic paralysis</td>
<td>AD</td>
<td>1a31-32</td>
<td>Dihydropyridate receptor</td>
</tr>
<tr>
<td>Schwartz-Jampel syndrome</td>
<td>Myotonia; dysmorphic</td>
<td>AR</td>
<td>1p34.1-36.1</td>
<td>Perlecan</td>
</tr>
<tr>
<td>(Chondrodystrophic myotonia)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rippling muscle disease</td>
<td>Muscle mounding/stiffness</td>
<td>AD</td>
<td>1q41, 3p25</td>
<td>Unknown Caveolin-3</td>
</tr>
<tr>
<td>Anderson’s syndrome</td>
<td>Periodic paralysis, cardiac arrhythmia, dysmorphic</td>
<td>AD</td>
<td>17q23</td>
<td>KCMJ2-Kir 2.1</td>
</tr>
<tr>
<td>Brody’s disease</td>
<td>Delayed relaxation, no myotonia</td>
<td>AR</td>
<td>16p12</td>
<td>Calcium-ATPase</td>
</tr>
<tr>
<td>Malignant hyperthermia</td>
<td>Anesthetic induced delayed relaxation</td>
<td>AD</td>
<td>19q13.1</td>
<td>Ryanodine receptor</td>
</tr>
</tbody>
</table>
secondary periodic paralyses, such as those due to thyrotoxicosis. In addition, it is reasonable to include the neuromuscular junction disorders in this pattern for completeness sake. In all of these conditions, the weakness can occur during or after exercise or often is unrelated to physical exertion.

Pattern 10: Stiffness and Decreased Ability to Relax

Pattern 10 is for all of the disorders that produce myotonia and paramyotonia. This includes the hereditary disorders involving sodium and chloride channelopathies (see Tables 18 and 19), as well as myotonic dystrophy types 1 and 2. Both myotonic dystrophies usually have fixed muscle weakness as well, often distal in dermatomyositis 1 (DM1) and proximal in DM2. The autosomal recessive form of chloride channelopathies, Becker’s disease, usually has fixed proximal weakness as well. In addition, a few other disorders can be put in this pattern. These include Brody’s disease, neuromyotonia, and the central nervous system disorder stiff-person syndrome (see Table 18).

LABORATORY APPROACH IN THE EVALUATION OF A SUSPECTED MYOPATHY

Creatine Kinase

Creatine kinase (CK) is the single most useful laboratory study for the evaluation of patients with a suspected myopathy. The CK is elevated in the majority of patients with muscle disease but may be normal in slowly progressive myopathies. The degree of CK elevation can also be helpful in distinguishing different forms of muscular dystrophy. For example, in DMD, the CK is invariably at least 10 times (and often up to 100 times) normal, whereas in most other myopathies there are lesser elevations. The other exceptions are LGMD 1C (caveolinopathy), 2A (calpainopathy), and 2B (dysferlinopathy) where the CK may also be markedly elevated. The CK level may not be elevated in some myopathies or may even be lowered by a number of factors including profound muscle wasting, corticosteroid administration, collagen diseases, alcoholism, or hyperthyroidism.

It is also important to remember that an elevation of serum CK does not necessarily imply a primary myopathic disorder (see Table 21). Many times the CK will rise modestly (usually to less than 10 times normal) in motor neuron disease and uncommonly, CK elevations may be seen in Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), or Charcot-Marie-Tooth (CMT) hereditary neuropathy. Endocrine disorders such as hypothyroidism and hypoparathyroidism can also be associated with high CK levels. Causes of CK elevation other than neuromuscular disease include: muscle trauma (falls, intramuscular or subcutaneous injections, needle EMG studies), viral illnesses, seizures, or strenuous exercise. In these cases, CK elevations are usually transient and less than five times normal.

Race and gender can also affect serum CK (see Table 22). CK levels are frequently above the “normal” range in some black individuals and in patients with enlarged muscles. Occasionally, benign elevations of CK appear on a hereditary basis. It is extremely unusual for a slightly elevated CPK (creatine phosphokinase), threefold or less, to be associated with an underlying myopathy in the absence of objective muscle weakness or pain.

Table 19 Pattern 10: Stiffness/decreased ability to relax

<table>
<thead>
<tr>
<th>Improves with exercise</th>
<th>Worsens with exercise/cold sensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myotonia – Na++ or Cl- channelopathy</td>
<td></td>
</tr>
<tr>
<td>Paramyotonia – Na++ channelopathy</td>
<td></td>
</tr>
<tr>
<td>Brody’s disease</td>
<td></td>
</tr>
<tr>
<td>With fixed weakness</td>
<td></td>
</tr>
<tr>
<td>Myotonic dystrophy (DM 1)</td>
<td></td>
</tr>
<tr>
<td>Proximal myotonic myopathy (DM 2)</td>
<td></td>
</tr>
<tr>
<td>Becker’s disease (AR Cl- channelopathy)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Rippling muscle</td>
<td></td>
</tr>
<tr>
<td>Malignant hyperthermia</td>
<td></td>
</tr>
<tr>
<td>Neuromyotonia</td>
<td></td>
</tr>
<tr>
<td>Stiff-person</td>
<td></td>
</tr>
</tbody>
</table>

AR = autosomal recessive, DM = dermatomyositis

Table 21 Differential diagnosis of creatine kinase elevation

<table>
<thead>
<tr>
<th>Myopathies</th>
<th>Neuropathies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscular dystrophies</td>
<td>Charcot-Marie Tooth</td>
</tr>
<tr>
<td>Congenital myopathies</td>
<td>Guillain-Barré syndrome</td>
</tr>
<tr>
<td>Metabolic myopathies</td>
<td>Others</td>
</tr>
<tr>
<td>Channelopathies</td>
<td>Viral illnesses</td>
</tr>
<tr>
<td>Inflammatory myopathies</td>
<td>Medications</td>
</tr>
<tr>
<td>Drug/toxin-induced</td>
<td>Surgery</td>
</tr>
<tr>
<td>Carrier state (dystrophinopathies</td>
<td>Trauma (needle EMG studies, IM or SQ injections)</td>
</tr>
<tr>
<td>Hypothyroidism/hypoparathyroidism</td>
<td>Strenuous exercise</td>
</tr>
<tr>
<td>Motor neuron diseases</td>
<td>Increased muscle mass</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>Race</td>
</tr>
<tr>
<td>Spinal muscular atrophy</td>
<td>Sex</td>
</tr>
<tr>
<td>Postpolio syndrome</td>
<td>“Idiopathic hyperCKemia”</td>
</tr>
</tbody>
</table>

EMG = electromyography, IM = intramuscular, SQ = subcutaneous

Serum tests for other muscle enzymes are significantly less helpful than the determination of the CK. Enzymes such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), and lactate dehydrogenase (LDH) may be slightly elevated in myopathies. Since AST, ALT, and LDH are often measured in screening chemistry panels, their elevation should prompt CK measurement to determine if the source is muscle or liver.
If a patient with an inflammatory myopathy is treated with an immunosuppressive agent that may cause hepatotoxicity, the liver specific enzyme, gamma glutamic transferase (GGT), should be followed.

In general, CK isoenzymes are not helpful in evaluating myopathies. CK-MM elevations are typical of muscle disease, but CK-MB is also elevated in myopathies and does not indicate that cardiac disease is present.

**Electrophysiologic Studies**

Electrodiagnostic (EDX) studies, consisting of both nerve conduction studies (NCS) and needle EMG should be part of the routine evaluation of a patient with a suspected myopathy. These studies are helpful in confirming that the muscle is indeed the correct site of the lesion and that weakness is not the result of an underlying motor neuron disease, neuropathy, or neuromuscular junction disorder. NCSs are typically normal in patients with myopathy. Needle EMG examination showing evidence of brief duration, small amplitude motor units with increased recruitment can be extremely helpful in confirming the presence of a myopathy. Needle EMG can also provide a clue as to which muscles have had recent or ongoing muscle injury and can be a guide as to which muscle to biopsy. It is important to realize, however, that the needle EMG can be normal in a patient with myopathy and the results of EDX studies need to be evaluated in the context of the patient’s history, neurological examination, and other laboratory studies.

**The Muscle Biopsy**

If the clinical and/or EDX features suggest the possibility of a myopathy, a muscle biopsy may be an appropriate test to confirm the diagnosis. However, many forms of hereditary muscle disorders can now be diagnosed with molecular genetic testing, eliminating the need for performing a muscle biopsy in every patient. A muscle specimen can be obtained through either an open or closed (needle or punch) biopsy procedure. The advantages of a needle or punch biopsy are that it is minimally invasive and cosmetically more appealing. In addition, multiple specimens can be obtained with a needle or punch biopsy. The disadvantage of

<table>
<thead>
<tr>
<th>Table 20</th>
<th>Clinical patterns of muscle disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weakness</td>
</tr>
<tr>
<td></td>
<td>Proximal</td>
</tr>
<tr>
<td>Pattern 1</td>
<td>Limb-girdle*</td>
</tr>
<tr>
<td>Pattern 2*</td>
<td>Distal</td>
</tr>
<tr>
<td>Pattern 3</td>
<td>Proximal arm/distal leg “scapuloperoneal”</td>
</tr>
<tr>
<td>Pattern 4</td>
<td>Distal arm/proximal leg</td>
</tr>
<tr>
<td>Pattern 5</td>
<td>Ptosis/ophthalmoplegia</td>
</tr>
<tr>
<td>Pattern 6*</td>
<td>Neck extensor</td>
</tr>
<tr>
<td>Pattern 7*</td>
<td>Bulbar (tongue, pharyngeal)</td>
</tr>
<tr>
<td>Pattern 8</td>
<td>Episodic weakness/ Pain/rhabdomyolysis + trigger</td>
</tr>
<tr>
<td>Pattern 9</td>
<td>Episodic weakness delayed or unrelated to exercise inability</td>
</tr>
<tr>
<td>Pattern 10</td>
<td>Stiffness/inability to relax</td>
</tr>
</tbody>
</table>

*Overlap patterns with neuropathy/motor neuron disease

ALS = amyotrophic lateral sclerosis, CPT = carnitine palmitoyltransferase, FSH= follicle-stimulating hormone, IBM = inclusion body myositis, INEM = isolated neck extensor myopathy, LEMS = Lambert-Eaton myasthenic syndrome, MG = myasthenia gravis, OPD = oculopharyngeal dystrophy
the closed biopsy procedure is that not all laboratories have the expertise to adequately process the muscle tissue acquired with this approach for all the necessary studies.

Selection of the appropriate muscle to biopsy is critical. Muscles that are severely weak (MRC grade 3 or less) should not be biopsied since the results are likely to show only evidence of “end-stage” muscle. In addition, muscles which have recently been studied by needle EMG should be avoided due to the possibility of artifacts created by needle insertion. Biopsies should generally be taken from muscles which demonstrate MRC grade 4 strength. For practical purposes, the biceps or deltoid are the muscles of choice in the upper extremities. In the lower extremities, the best choice is the vastus lateralis. The gastrocnemius should be avoided since its tendon insertion extends throughout the muscle and inadvertent sampling of a myotendinous junction may cause difficulty with interpretation. Occasionally, imaging procedures such as muscle ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) can be used to guide selection of the appropriate muscle to biopsy.

Biopsy specimens can be analyzed by light microscopy, electron microscopy, biochemical studies, and immune staining (see Table 23). In most instances, light microscopic observations of frozen muscle tissue specimens are sufficient in making a pathologic diagnosis. Typical myopathic abnormalities include central nuclei, both small and large hypertrophic round fibers, split fibers, and degenerating and regenerating fibers. Inflammatory myopathies are characterized by the presence of mononuclear inflammatory cells in the endomysial and perimysial connective tissue between fibers and occasionally around blood vessels. In addition, atrophy of fibers located on the periphery of a muscle fascicle, perifascicular atrophy, is a common finding in DM. Chronic myopathies frequently show evidence of increased connective tissue and fat.

For general histology, the hematoxylin and eosin (H&E) and modified Gomori trichrome are the most useful. The latter is particularly helpful in identifying ragged-red fibers, which might suggest a mitochondrial disorder. In addition to these standard stains, other histochemical reactions can be used to gain additional information (see Table 25). The myosin ATPase stains (alkaline: pH 9.4; acidic: pH 4.3 and 4.6) allow a thorough evaluation of histochemistry fiber types. Type 1 fibers (slow-twitch, fatigue-resistant, oxidative metabolism) stain lightly at acidic pHs. Normally, there is a random distribution of the two fiber types and there are generally twice as many type 2 as type 1 fibers. In a number of myopathies, there is a nonspecific type 1 fiber predominance. Oxidative enzyme stains (NADH dehydrogenase, succinate dehydrogenase, cytochrome-c oxidase) are useful for identifying myofibrillar and mitochondrial abnormalities. Stains for Periodic acid-Schniff (PAS) stains can be assayed with Congo red or crystal violet staining. Finally, immunohistochemical techniques can stain for muscle proteins that are deficient in some muscular dystrophies (e.g., dystrophin in DMD and BMD) or for products that are increased in certain inflammatory myopathies, such as the membrane attack complex in dermatomyositis.

Electron microscopy (EM) evaluates the ultrastructural components of muscle fibers and is not required in the majority of myopathies to make a pathologic diagnosis. EM is important, however, in the diagnosis of some congenital myopathies and mitochondrial disorders. Findings detected only by EM are seldom of clinical importance.

<table>
<thead>
<tr>
<th>Table 22</th>
<th>Effect of race and gender on creatine kinase measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>Constituents</td>
</tr>
<tr>
<td>High</td>
<td>Black males</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Nonblack males</td>
</tr>
<tr>
<td>Low</td>
<td>Nonblack females</td>
</tr>
<tr>
<td><strong>ULN</strong></td>
<td>Upper limits of normal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 23</th>
<th>Utility of muscle biopsy stains and histochemical reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histochemical reactions and stains</strong></td>
<td><strong>Clinical utility</strong></td>
</tr>
<tr>
<td>Hematoxylin and eosin</td>
<td>General histology</td>
</tr>
<tr>
<td>Gomori trichrome</td>
<td>General histology and mitochondrial disease</td>
</tr>
<tr>
<td>ATPase</td>
<td>Distribution of fiber types</td>
</tr>
<tr>
<td>NADH, SDH, cytochrome oxidase</td>
<td>Myofibrillar and mitochondrial abnormalities</td>
</tr>
<tr>
<td>Periodic acid-Schniff</td>
<td>Glycogen storage diseases</td>
</tr>
<tr>
<td>Oil Red O</td>
<td>Lipid storage diseases</td>
</tr>
<tr>
<td>Congo red, crystal violet</td>
<td>Detection of amyloid deposition</td>
</tr>
<tr>
<td>Myophosphorylase</td>
<td>McArdle’s disease</td>
</tr>
<tr>
<td>Phosphofructokinase</td>
<td>Phosphofructokinase deficiency</td>
</tr>
<tr>
<td>Myoadenylate deaminase</td>
<td>Myoadenylate deaminase deficiency</td>
</tr>
<tr>
<td>Dystrophin immunostain</td>
<td>Duchenne and Becker MD muscular dystrophy</td>
</tr>
<tr>
<td>Dysferlin immunostain</td>
<td>Limb-girdle MD 2B</td>
</tr>
<tr>
<td>Membrane attack complex immunostain</td>
<td>Dermatomyositis</td>
</tr>
<tr>
<td><strong>MD</strong> = muscular dystrophy, <strong>NADH</strong> = nicotinamide adenine dinucleotide plus hydrogen, <strong>SDH</strong> = succinate dehydrogenase</td>
<td></td>
</tr>
</tbody>
</table>
The muscle tissue can also be processed for biochemical analysis to determine a specific enzyme defect in the evaluation of a possible metabolic or mitochondrial myopathy. In addition, Western blot determinations from muscle tissue can be performed for certain muscle proteins. This type of analysis is usually limited to the dystrophin assays when the immunostains and the molecular genetic studies are inconclusive in establishing a diagnosis of either DMD or BMD.

### Molecular Genetic Studies

The specific molecular genetic defect is now known for a large number of hereditary myopathies, and mutations can be identified by peripheral blood deoxyribonucleic acid (DNA) analysis. Molecular genetic studies which are commercially available are included in Table 24. Molecular genetic testing frequently eliminates the need for muscle biopsy. This technology is also extremely helpful for determining carrier status and for performing prenatal testing.

### Other Tests

In addition to CK determinations, additional blood tests that can be extremely helpful in the evaluation of a patient with a suspected myopathy include serum electrolytes, thyroid function tests, parathyroid hormone levels, and human immunodeficiency virus (HIV). In patients with an inflammatory myopathy, serologic determinations for systemic lupus erythematosus, rheumatoid arthritis, and other immunologic markers (e.g., Jo-1 antibodies) can occasionally be useful. A urine analysis can also be performed to detect the presence of myoglobinuria. This should be suspected if the urine tests positive for blood but no red blood cells are identified.

Forearm exercise testing can be a critical part of the evaluation of a patient with a suspected metabolic myopathy. The exercise test should be carried out without the blood pressure cuff since ischemic exercise may be hazardous in patients with defects in the glycolytic enzyme pathway. The test is performed by asking the patient to perform isometric contractions using a hand grip dynamometer for 1.5 seconds separated by rest periods of 0.5 seconds for 1 minute. A resting blood sample for venous lactate and ammonia is obtained at baseline and subsequently at 1, 2, 4, 6, and 10 minutes following the completion of exercise. A threefold increase in lactate level represents a normal response. The characteristic elevation of serum lactate after exercise is absent (phosphofructokinase deficiency, myophosphorylase deficiency) or reduced (phosphoglycerase mutase deficiency). Forearm testing is normal in all disorders of fat metabolism and also in some glycolytic disorders with fixed muscle weakness, such as acid maltase deficiency.

### CONCLUSION

While this “pattern recognition approach” to myopathy may have limitations, it can be extremely helpful in narrowing the differential diagnosis and, therefore, minimizing the number of laboratory studies which must be ordered to confirm the diagnosis. There will always be patients with muscle disease who will not fit neatly into any of these six categories. In addition, patients with involvement of other areas of the neuroaxis such as the motor neuron, peripheral nerve, or neuromuscular junction, may also frequently present with one of these patterns. For example, while proximal greater than distal weakness is most often seen in a myopathy, patients with acquired demyelinating neuropathies (GBS and CIDP) often have proximal as well as distal muscle involvement. Careful consideration of the distribution of muscle weakness and attention to these common patterns of involvement in the context of other aspects of the neurologic examination and laboratory evaluation will usually, however, lead the clinician to a timely and accurate diagnosis.

### REFERENCES


<table>
<thead>
<tr>
<th>Table 24</th>
<th>Commercially available molecular genetic studies performed with peripheral blood samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne and Becker MD</td>
<td></td>
</tr>
<tr>
<td>Facioscapulohumeral MD</td>
<td></td>
</tr>
<tr>
<td>Myotonic dystrophy (Types 1 and 2)</td>
<td></td>
</tr>
<tr>
<td>Oculopharyngeal MD</td>
<td></td>
</tr>
<tr>
<td>Limb-girdle MD 1B, 2A, 2C-F, and 2I</td>
<td></td>
</tr>
<tr>
<td>Congenital MD (FKRP, FCMD, MEB and POMT1 mutations)</td>
<td></td>
</tr>
<tr>
<td>Nonaka myopathy/inclusion body myopathy type 2</td>
<td></td>
</tr>
<tr>
<td>Nemaline myopathy (ACTA1 mutations)</td>
<td></td>
</tr>
<tr>
<td>Myotubular myopathy (MTM1 mutations)</td>
<td></td>
</tr>
<tr>
<td>Myoclonic epilepsy and ragged red fibers (MERRF)</td>
<td></td>
</tr>
<tr>
<td>Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS)</td>
<td></td>
</tr>
</tbody>
</table>

MD = muscular dystrophy, FCMD = Fukuyama congenital muscular dystrophy, FKRP = fukutin-related protein, MEB = muscle-eye-brain disease, POMT1 = protein-O-mannosyltransferase 1
The Autoimmune Myopathies: Diagnosis and Treatment

Andrew L. Mammen, MD, PhD
Co-Director, Johns Hopkins Myositis Center
Assistant Professor
Departments of Neurology and Medicine
The Johns Hopkins Bayview Medical Center
Baltimore, Maryland

EPIDEMIOLOGY

The autoimmune myopathies are a rare, heterogeneous group of acquired muscle diseases which, taken together, have an approximate prevalence 22 per 100,000. Dermatomyositis (DM), polymyositis (PM), and immune-mediated necrotizing myopathy (IMNM) are the three most common forms of autoimmune muscle disease. In adults, the peak incidence of autoimmune myopathy is between 45 and 60 years of age but can occur in younger and older patients as well. In children, only DM is well described; PM and IMNM occur much less frequently, if at all, in this age group.

Genetic factors predisposing individuals to developing autoimmune myopathy have been identified (e.g., specific human leukocyte antigen alleles). However, the link between any single gene and the development of autoimmune myopathy is relatively weak. As a result, multiple cases of PM, DM, and IMNM are very rarely found in a single family; the presence of muscle disease in more than one family member should strongly suggest the presence of an inherited myopathy.

Although the initiation of autoimmune myopathy is thought to result from the interaction between genetic and environmental risk factors, very few environmental risk factors are known. However, geographic and demographic analyses have established that those exposed to higher levels of ultraviolet light exposure are more prone to developing DM. In addition, recent studies strongly suggest that in rare cases, statin exposure may trigger an IMNM10,16 associated with antibodies recognizing HMG-CoA reductase (HMGCR).

SYMPTOMS AND SIGNS

The majority of patients with autoimmune myopathy present with symmetric proximal muscle weakness, with or without muscle pain, progressing over weeks or months. These patients often complain of difficulty with stairs, require the use of their arms to rise from low chairs, and may have difficulty keeping their arms above their heads. In severe cases, pharyngeal weakness may require the placement of a feeding tube. Similarly, diaphragmatic weakness may lead to mechanical ventilation. In general, distal weakness occurs only in the context of more severe proximal muscle weakness. Prominent distal weakness, facial weakness, and scapular winging are rarely seen in patients with autoimmune myopathy and should alert the examiner to the possibility of an alternative diagnosis, such as one of the genetic muscle diseases or inclusion body myositis (IBM).

The clinical manifestations of IMNM are most often restricted to skeletal muscle. In contrast, both DM and PM are systemic autoimmune diseases that frequently involve other organ systems. Particularly in those with the antisynthetase syndrome (see below), dyspnea may occur as a result of interstitial lung disease (ILD). In contrast to those with diaphragmatic weakness alone, patients with ILD frequently present with a persistent dry cough, crackles on chest auscultation, and activity-dependent decreases in oxygen saturation. In addition to severe fatigue, arthritis, Raynaud’s phenomenon, fevers, and cardiac abnormalities also are possible systemic manifestations of PM and DM. In some patients, DM or PM occurs in the context of another well-defined systemic autoimmune disease, such as systemic lupus erythematosus, rheumatoid arthritis, or scleroderma.
The cutaneous manifestations of DM may occur either before or after weakness is noticed. Furthermore, in cases of “amyopathic” DM, typical skin features are found in the absence of clinically apparent muscle involvement (although muscle biopsy, needle electromyography [EMG], or thigh magnetic resonance imaging [MRI] may reveal subtle evidence of muscle disease). The two pathognomonic skin findings of DM are Gottron’s papules and the heliotrope rash.59 The former are raised erythematous lesions localized to the extensor surfaces of the metacarpophalangeal, proximal interphalangeal, and/or distal interphalangeal joints. In Caucasians, the heliotrope rash can be recognized as a purplish discoloration of the eyelids, whereas, in African Americans, the heliotrope rash may appear as a hyperpigmented rash in the same distribution. Other dermatologic features are not specific to DM. These include erythematous or poikilodermatous rashes on the posterior neck and shoulders (shawl sign), the anterior neck (V-sign), and/or the lateral thighs (holster sign). The nail-fold changes often in seen in scleroderma, including erythema and capillary drop-out, are characteristic of DM as well. Other patients, especially those with the antisynthetase syndrome, develop a condition known as “mechanic’s hands”; these hyperkeratotic skin thickenings on the radial surface of the fingers may crack and be associated with significant pain.

LABORATORY FINDINGS

Muscle Enzymes

Serum levels of muscle enzymes typically are elevated in patients presenting with one of the autoimmune myopathies. These include creatine kinase (CK), aldolase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH). While all of these enzymes may be elevated in a single patient, this is not always the case. For example, a series of patients with features of autoimmune myopathy who presented with elevated aldolase and normal CK levels was recently described.15 Furthermore, a minority of patients presenting with weakness and other clinical evidence of autoimmune myopathy (especially DM) may have normal muscle enzyme levels. Finally, it is important to recognize that AST and ALT, widely referred to as “liver enzymes,” are released from damaged muscle cells as well. When confusion arises as to the origin of AST and ALT elevations, it may be helpful to check a serum gamma-glutamyl transpeptidase (GCT), which is frequently released from damaged liver but not muscle.19

Autoantibodies

Approximately two-thirds of patients with autoimmune myopathy will have one of the approximately 15 currently identified “myositis-specific” autoantibodies (MSAs).15 These antibodies are found in patients with PM, DM, and IMNM, but not in patients with other defined rheumatic or neuromuscular diseases. Each MSA is associated with a distinct clinical phenotype, allowing for the grouping of the antibodies into three categories: antisynthetase antibodies, DM-associated antibodies, and IMNM-associated antibodies.

Antibodies recognizing histidyl-tRNA synthetase (i.e., Jo-1) are among the most common of the MSAs, being found in about 20% of those with an autoimmune myopathy. Patients with antibodies recognizing Jo-1 or one of the other seven tRNA synthetases targeted by the immune system frequently have the antisynthetase syndrome, which includes two or more of the following features: autoimmune myopathy (either DM or PM), ILD, nonerosive arthritis, Raynaud’s phenomenon, mechanic’s hands, and fevers. Some patients may have ILD or other features of the antisynthetase syndrome without developing a myopathy.

Among the DM-associated antibodies, anti-Mi-2 is the most common and is found in approximately 15% of DM cases. Those with antibodies against this chromatin-remodeling enzyme have more fulminating initial cutaneous manifestations, but they also have a better response to therapy compared to anti Mi-2 negative DM patients. Interestingly, anti-Mi-2 antibodies also are associated with a decreased risk of malignancy compared to those DM patients without these antibodies. In contrast, patients with the DM-associated antibodies recognizing the p155/140 antibody are at a substantially increased risk of developing malignancy. Other DM-associated autoantibodies include those recognizing MDA5 (associated with amyopathic DM), SUMO-1, and NXP-2. However, these less commonly found MSAs are not currently commercially available.

IMNM-associated antibodies include those recognizing the signal recognition particle (SRP) and HMGCR. As the name suggests, muscle biopsies from patients with these antibodies are often distinguished by myofiber degeneration, necrosis, myophagocytosis, and/or regeneration in the absence of prominent lymphocytic infiltrates. Anti-SRP antibodies are found in about 5% of autoimmune myopathy patients, many of whom have very high CK levels (>10,000 IU/L), rapidly progressive weakness, early muscle atrophy, dysphagia, and an incomplete response to immunosuppressive therapy. Anti-HMGCR antibodies are also found in approximately 5% of patients with autoimmune myopathy. In the author’s cohort of autoimmune myopathy subjects, approximately 75% of anti-HMGCR–positive patients developed myalgias and muscle weakness during the course of treatment with statin medications. In those anti-HMGCR patients age 50 years or older, approximately 90% had a prior statin exposure; statin exposure was only approximately 25% with DM and approximately 35% with PM in age-matched subjects. Unlike those with self-limited statin myopathy, muscle weakness in anti-HMGCR myopathy progresses even after statins are discontinued and requires immunosuppressive therapy to control. To date, commercial testing for anti-HMGCR antibodies is not available.

MAGNETIC RESONANCE IMAGING

In some cases, muscle magnetic resonance imaging (MRI) with T1 and short tau inversion recovery (STIR) may help in the diagnosis and management of patients with autoimmune myopathy.1 T1 imaging is particularly useful for identifying the fatty replacement of muscle which may occur in patients with chronic, incompletely treated muscle disease. In contrast, STIR sequences reveal the muscle edema often associated with active inflammation and/or necrosis. STIR imaging also can identify fasciitis. Because autoimmune myopathies may dramatically affect some muscles while sparing others which are part of the same group (e.g., rectus femoris versus vastus lateralis), MRI can help select an affected
muscle for biopsy. In some cases, MRI may help guide therapeutic decisions. For example, in this author’s view, immunosuppressive therapy may improve weakness resulting from active disease visualized on STIR sequences, but it is unlikely to reverse weakness associated with severe fatty replacement of muscle tissue.

NEEDLE ELECTROMYOGRAPHY

In patients with suspected autoimmune myopathy, needle electromyography (EMG) should be performed unilaterally, so as to spare the contralateral muscle for possible biopsy. As in other myopathic processes, needle EMG typically reveals the early recruitment of small polyphasic motor unit potentials. In those muscles with active myofiber necrosis, spontaneous activity in the form of fibrillations and positive sharp waves may be observed. Importantly, spontaneous activity may be absent in some untreated autoimmune myopathy patients, especially those with DM, as well as in those with partially treated disease.

MUSCLE BIOPSY

Although some would debate its utility in patients presenting with pathognomonic cutaneous manifestations of DM, a muscle biopsy should be considered as part of the initial workup of all patients with suspected autoimmune myopathy in order to establish the presence of characteristic findings and exclude the possibility of some other nonimmune-mediated myopathic process. The biceps, deltoid, and quadriceps are most frequently targeted for muscle biopsy given their proximal location and accessibility to the surgeon. In general, a muscle with strength graded in the 4/5 range may be most likely to yield a diagnostically-useful biopsy specimen; weaker muscles more frequently include “end-stage” muscle with fewer distinguishing features. If needle EMG revealed evidence of an irritable myopathy on one side, biopsy of the same muscle on the contralateral side should be considered. As discussed above, MRI also may help select a muscle with significant STIR hyperintensity, suggesting the presence of active inflammation or muscle necrosis.

Typical biopsy features associated with autoimmune myopathies include those seen in other myopathic processes: degenerating or necrotic fibers, regenerating fibers, atrophic myofibers, and the presence of inflammatory cells within the endomysium, perimysium, or perivascular regions. Where available, immunostaining may reveal the presence of CD8+ T cells surrounding and invading non-necrotic muscle fibers (i.e., primary inflammation) or the upregulation of major histocompatibility complex (MHC) class I molecules within myofibers. However, these features also are characteristic of IBM, a disease with poor, if any, response to immunosuppression. In contrast to these nonspecific muscle biopsy features, perifascicular atrophy virtually confirms the diagnosis of dermatomyositis. Other special immunostaining results may be specific for autoimmune myopathies (e.g., increased perifascicular expression of MxA protein is seen only in DM12), but these tests are not typically available outside of specialized research laboratories.

DIFFERENTIAL DIAGNOSIS

Distinguishing the autoimmune myopathies from nonimmune-mediated myopathic processes is crucial because only patients with the former are likely to have a sustained benefit from immunosuppressive therapy. In patients with proximal muscle weakness, a definite diagnosis of DM may be secured with elevated CK levels, an irritable myopathy on needle EMG, and Gottron’s sign or a heliotrope rash. However, only after careful consideration of the history, physical examination findings, laboratory results, and muscle biopsy findings have excluded the possibility of other myopathies should a diagnosis of PM or IMNM be made.

Although genetic susceptibility factors for autoimmune myopathies do exist, these are rightly considered to be acquired myopathies and it is extremely rare for two family members to be affected. Consequently, when the family history is notable for another family member with PM, one of the inherited myopathies is most likely the correct diagnosis. Dystrophinopathy, facioscapulohumeral dystrophy (FSHD), calpainopathy (limb-girdle muscular dystrophy 2A [LGMD2A]), and dysferlinopathy (LGMD2B) are among the muscular dystrophies which commonly include inflammatory cells on muscle biopsy and may be misdiagnosed as PM.

Of all myopathies, IBM is the one most commonly mistaken for PM. Distinguishing these two diseases is important as IBM responds poorly, if at all, to treatment with steroids (which may cause more harm than good) and other immunosuppressive agents.

Confusion may arise because both IBM and PM share certain muscle biopsy findings, including abundant primary inflammation and upregulation of MHC I. While the presence of red-rimmed vacuoles on Gomori trichrome staining characterizes many IBM muscle biopsies and is not seen in PM, this feature may be missed by the pathologist and, in fact, may be absent in as many as one-third of patients with an IBM phenotype.

IBM most frequently affects males over the age of 50 and should always be at the top of the differential diagnosis in this group of patients. In contrast to those with DM, PM, or IMNM, patients with IBM often report the slow progression of weakness, symptoms of hand weakness or foot-drop, dysphagia, and poor response to trials of immunosuppressive therapy. On physical examination, IBM patients have asymmetric weakness of muscles in the forearm flexor compartment which mediate wrist flexion and distal finger flexion, with relative sparing of the wrist and finger extensors. Asymmetric weakness and atrophy of the quadriceps with relatively preserved hamstring strength is another characteristic feature of IBM. Deltoids are often only affected late in the course of IBM, whereas weakness of the obicularis oculi and tibialis anterior muscles may occur early. When typical IBM physical examination features are present in a patient over age 50, the diagnosis of IBM is usually certain even if the muscle biopsy reveals only inflammation with no rimmed vacuoles.

On physical examination, the presence of scapular winging always should be assessed since this is rarely found in the autoimmune myopathies. Rather, its presence should suggest the possibility of FSHD, LGMD2A, Emery-Dreifuss muscular dystrophy, or one of the scapuloperoneal syndromes (e.g., centronuclear myopathy).
Similarly, facial weakness is a rare manifestation of PM, DM, or IMNM and should suggest an alternative diagnosis such as FSHD or IBM.

TREATMENT

Immunosuppressive therapies are the mainstay of treatment for the autoimmune myopathies. Because few prospective randomized trials have been conducted in DM, PM, and IMNM, approaches to treatment are based primarily on retrospective studies (many suboptimally designed) and expert opinion. As a general rule, the physician’s role in managing these patients is to help restore strength to weak patients. In many cases, CK levels will decline to normal levels with effective treatment. However, some patients will regain full strength even though CK levels may not normalize. In this author’s view, tapering of immunosuppression should commence when strength is fully restored, even if the CK level remains elevated. Conversely, some patients with autoimmune myopathy, especially DM, will experience flares of muscle weakness in the absence of CK elevations. These patients should be treated accordingly. Similarly, in patients with systemic autoimmune disease, involvement of other organ systems may drive therapeutic decisions even when muscle strength remains normal. For example, escalating immunosuppression may be warranted in patients with good strength but persistent ILD or skin rash.

Corticosteroids

Corticosteroids generally are used as the initial therapy. Oral prednisone may be started at a dose of 1 mg/kg/day and tapered as tolerated once normal muscle strength has been restored. The author often tapers prednisone by 10 mg/day every 3 weeks until reaching a dose of 30 mg/day, then tapers by 5 mg/day every 3 weeks until reaching a dose of 20 mg/day, and then, finally, tapers by 2.5 mg/day every 3 weeks until reaching the lowest possible tolerated dose. To prevent bone loss, patients on prednisone should take 800 IU of vitamin D and 1,000 mg of calcium each day. Prophylaxis against Pneumocystis jiroveci pneumonia in patients on doses of prednisone greater than 20 mg/day should be considered. Gastrointestinal (GI) prophylaxis with a proton pump inhibitor is also recommended. In patients who remain or become weak on high-dose steroids, particularly in those whose CK levels are normalizing, the possibility of steroid-induced myopathy should be kept in mind. In patients with rapidly progressive weakness, particularly those who develop dysphagia or respiratory failure, many experienced clinicians will initiate corticosteroid therapy with intravenous methylprednisolone at a dose of 1 g/day for 3-5 days and then start high-dose oral prednisone. Patients who flare on prednisone doses of 10 mg/day or more usually require a steroid-sparing medication to reduce the risk of comorbidities associated with longterm steroid use.

Methotrexate

Methotrexate is a common first-line steroid sparing medication, particularly in those who experience significant arthralgias or arthritis with their disease. Methotrexate may be started at 10-15 mg once per week by mouth and the dose increased as needed by 2.5 mg each week until reaching a maximum weekly dose of 25 mg. To avoid GI side effects, folic acid at a dose of 1 mg/day should be given. In those who cannot tolerate oral methotrexate due to GI side effects, weekly subcutaneous administration at the same dose very often eliminates this problem. Given the potential for liver toxicity, liver function tests should be monitored and patients should be advised against drinking alcohol while on methotrexate. Because pneumonitis is a potential side-effect of methotrexate, patients should be advised to report the development of persistent cough or shortness of breath. Because methotrexate-induced pneumonitis may be difficult to distinguish from ILD, some clinicians avoid its use in patients with known lung involvement or antisynthetase antibodies. Given its teratogenic potential, methotrexate is absolutely contraindicated in pregnancy and women who take this medication are advised to use effective birth control.

Azathioprine

Azathioprine often is used as a steroid-sparing agent in patients with autoimmune myopathy. Some patients are unable to metabolize azathioprine and are likely to suffer serious bone marrow toxicity when using conventional doses of this medication. Consequently, this author does not initiate azathioprine therapy until the patient has been tested for the thiopurine methyltransferase (TPMT) deficiency, either by enzyme activity or gene test. In patients with normal TPMT levels, azathioprine may be initiated at a dose of 50 mg/day and increased by 50 mg every 2 weeks until reaching a dose of 2-2.5 mg/kg/day. Liver enzymes and blood counts should be followed monthly to monitor for evidence of bone marrow suppression and hepatic toxicity. Other potential toxicities include pancreatitis, teratogenicity, and increased risk of malignancy, especially lymphoma.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIg) may be effective as a steroid-sparing agent and generally is safest to use in patients who are not elderly or have a prior history of stroke, myocardial infarction, deep vein thrombosis, renal insufficiency, or immunoglobulin A (IgA) deficiency. IVIg is given typically every 4 weeks at a dose of 2 g/kg divided over 3 to 5 days. Along with corticosteroids, IVIg is a therapy of choice in patients who require immunosuppressive therapy during pregnancy. Complications include infusion reactions, renal toxicity, thromboembolic events, and aseptic meningitis.

Mycophenolate Mofetil

Mycophenolate mofetil may be used as a steroid-sparing medication in patients with autoimmune myopathy and is favored by this author in patients with pre-existing liver disease because of its lack of hepatic toxicity. A starting dose of 500 mg twice a day by mouth can be increased over several weeks in increments of 500 mg to doses as high as 1,500 mg twice each day. GI side-effects are relatively common and blood counts should be monitored for evidence of bone marrow toxicity. Progressive multifocal leukoencephalopathy is a rare but fatal infectious complication of mycophenolate mofetil.
Refractory Disease

In patients with refractory disease, the possibility that the patient may not have a primary immune-mediated process should be considered. For example, many clinicians have observed that patients who initially present with features characteristic of PM may convert to an IBM phenotype that is unresponsive to aggressive immunosuppressive treatment. In these cases, it may be prudent to taper immunosuppressive medications in order gauge whether they are actually helping. A careful review of the patients’ medication list should be undertaken to look for the presence potentially myotoxic medications (e.g., statins, colchicine, or plaquenil). In some cases, a repeat biopsy may be performed. If an autoimmune myopathy is still suspected, the use of alternative agents should be considered. These include cyclophosphamide (especially in those with refractory ILD), rituximab, tumor necrosis factor inhibitors (e.g., etanercept), and cyclosporine.

REFERENCES

INTRODUCTION

In 1954, Walton and Nattrass\(^1\) established the diagnostic category of limb-girdle muscular dystrophy (LGMD). They designated criteria distinguishing cases of muscular dystrophy with proximal extremity weakness and no facial involvement from Duchenne, facioscapulohumeral and myotonic muscular dystrophies. Major breakthroughs in molecular biology and genetics the last 2 decades continue to broaden the understanding of these conditions.

The LGMDs may be autosomal dominant (LGMD1) or autosomal recessive (LGMD2). Overlaid on this is a lettering system delineating the order in which each chromosomal locus was discovered (Table 1). Phenotypic variability within genetic subtypes has led to another classification system based on gene defects. Thus, all myopathies with mutations in the gene for dysferlin also fall under the moniker of dysferlinopathies.

The prevalence of LGMDs is estimated around 2 to \(3 \times 10^{-5}\).\(^2\) In large referral centers, a specific genetic diagnosis can be made in 60-80% of LGMD cases.\(^3\) LGMDs stem from protein defects throughout the myofiber including the nucleus, sarcoplasm, sarcomere, sarcolemma, and the extracellular domain. The differential diagnosis of the LGMDs includes muscle diseases with prominent proximal upper and lower extremity weakness such as dystrophinopathies; Bethlem myopathy; myotonic dystrophy type 2; the metabolic, mitochondrial, myofibrillar, and congenital myopathies; and cases of facioscapulohumeral muscular dystrophy sans facial involvement.\(^3\)

AUTOSOMAL DOMINANT LIMB-GIRDLE MUSCULAR DYSTROPHY

In general, autosomal dominant LGMDs are less common and have lower creatine kinase (CK) levels (Tables 1 and 2).

LGMD1A—Myotilin

LGMD1A accounts for less than 2% of LGMD cases with most myotilinopathies presenting as distal myopathies. LGMD1A patients typically present between 15-35 years of age with proximal, or proximodistal, leg weakness. Subsequent involvement spreads to the proximal upper extremities and distal limbs. The ability to walk is rarely affected early in the course, but steady disease progression may leave patients wheelchair dependent 20 years after symptom onset. Heel cord contractures and reduced elbow, knee, and ankle muscle stretch reflexes are common. Distinctive nasal dysarthria and hypophonia is an exceptional feature in some LGMD1A family members.\(^4\)

CK levels are normal to tenfold normal. Needle electromyography (EMG) indicates a primary myopathy, with occasional irritability. Muscle biopsy reveals mild, nonspecific dystrophic features, autophagic vacuoles, and Z-band streaming. As one of the myofibrillar myopathies, myotilinopathy biopsies may demonstrate desmin-positive aggregates via immunostaining. Molecular analysis via gene sequencing is commercially available for the causative gene, \((MYOT)\) located on chromosome 5q31.
Treatment consists of supportive services and range of motion exercises. Evaluation of pharyngeal function through video fluoroscopy enables decisions about the safety of oral feeding. Some patients eventually require percutaneous gastrointestinal feeding devices.

**LGMD1B—Lamin A/C**

Mutations in the LMNA gene cause a panoply of human disease. Nonskeletal muscle disorders include: Dunnigan familial partial lipodystrophy; autosomal recessive, axonal, peripheral polyneuropathy; autosomal dominant, axonal, peripheral polyneuropathy with or without leuconychia; mandibuloacral dysplasia; Hutchinson-Gilford progeria syndrome; dilated cardiomyopathy; heart-hand syndrome of the Slovenian type; fatal, infantile, restrictive dermopathy; and metabolic syndrome. Syndromes with skeletal muscle involvement include: LGMD1B, autosomal dominant and recessive Emery-Dreifuss muscular dystrophy (EDMD), congenital muscular dystrophy, and autosomal dominant dilated cardiomyopathy with atroventricular block. The skeletal muscle phenotypes are overlapping syndromes exhibiting greater or lesser degrees of muscle weakness, joint contractures, and cardiac dysfunction. LGMD1B manifests proximal weakness with fewer joint contractures and variable cardiac manifestations.

Lamin A/C is a nuclear envelope protein like emerin, thus it is not surprising that one of the phenotypes closely mimics X-linked EDMD. Lamin A/C associated diseases form an overlapping spectrum, not unlike multiple overlapping, three dimensional Venn diagrams. Identical mutations in the lamin A/C gene have presented within one family as lipodystrophy with cardiac and skeletal muscle symptoms in one sibling and only mild EDMD-like weakness with early onset cardiac arrhythmias in another. Nonpenetration from generation to generation is not uncommon for the various laminopathy phenotypes.

Clinical onset of LGMD1B may occur in the first decade and even as a congenital syndrome, but it also begins in the 20s, 30s or 40s. Symmetric, proximal, lower extremity weakness predominates, eventually extending to the proximal upper extremities and the distal lower extremities. The biceps appear preferentially affected earlier and more severely than shoulder girdle muscles. Joint contractures, although often subtle, are almost always present, with elbow and neck flexors more so affected than ankle, knee, hip, and wrist joints. Slow progression relegates few patients into wheelchairs. Laminopathies constitute 3-5% of LGMD patients. Cardiac involvement often begins in the second and third decade, independent of skeletal muscle involvement. Cardiac manifestations include early dysrhythmias and conduction block, while dilated cardiomyopathy comes later in the course. Arrhythmias requiring pacemaker placement affect most patients by their 20s. Progressive heart failure responds to cardiac transplantation.

Serum CK values range up to 10 times normal. Needle EMG yields myopathic motor units. Muscle biopsies show variability in fiber size, increased internal nuclei, fiber splitting, and mild-to-moderate connective tissue replacement and fatty infiltration. Electron microscopy reveals abnormal distribution of heterochromatin in nuclei of muscle fibers and satellite cells. Muscle is not readily stained for lamin A/C, thus DNA analysis is required for definitive diagnosis. Gene sequencing is commercially available from a number of sources.

---

**Table 1. The limb girdle muscular dystrophies: genetic information**

<table>
<thead>
<tr>
<th>LGMD</th>
<th>Protein</th>
<th>Gene</th>
<th>Linkage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Myotilin</td>
<td>MYOT</td>
<td>5q22.3-31.3</td>
</tr>
<tr>
<td>1B</td>
<td>Lamin A/C</td>
<td>LMNA</td>
<td>1q11-21</td>
</tr>
<tr>
<td>1C</td>
<td>Caveolin-3</td>
<td>CAV3</td>
<td>3p25</td>
</tr>
<tr>
<td>1D</td>
<td>Unknown</td>
<td>Unknown</td>
<td>6q23</td>
</tr>
<tr>
<td>1E</td>
<td>Unknown</td>
<td>Unknown</td>
<td>7q</td>
</tr>
<tr>
<td>1F</td>
<td>Unknown</td>
<td>Unknown</td>
<td>7q21-32.2</td>
</tr>
<tr>
<td>1G</td>
<td>Unknown</td>
<td>Unknown</td>
<td>4p21</td>
</tr>
<tr>
<td>1H</td>
<td>Unknown</td>
<td>Unknown</td>
<td>3p23-2p25</td>
</tr>
<tr>
<td>2A</td>
<td>Calpain-3</td>
<td>CAPN3</td>
<td>15q15.1</td>
</tr>
<tr>
<td>2B</td>
<td>Dysferlin</td>
<td>DYSF</td>
<td>2p13</td>
</tr>
<tr>
<td>2C-F</td>
<td>γ, α, β, δ-sarcoglycan</td>
<td>SGCG,A,B,D</td>
<td>13q-17q-4q-5q</td>
</tr>
<tr>
<td>2G</td>
<td>Telethonin</td>
<td>TCAP</td>
<td>17q11-q12</td>
</tr>
<tr>
<td>2H</td>
<td>Tripartite-motif containing gene 32</td>
<td>TRIM32</td>
<td>9q31-34</td>
</tr>
<tr>
<td>2I</td>
<td>Fukutin-related protein</td>
<td>FKRP</td>
<td>19q13.3</td>
</tr>
<tr>
<td>2J</td>
<td>Titin</td>
<td>TTN</td>
<td>2q31</td>
</tr>
<tr>
<td>2K</td>
<td>O-mannosyltransferase-1</td>
<td>POMT1</td>
<td>9q34.1</td>
</tr>
<tr>
<td>2L</td>
<td>Anoctamin</td>
<td>ANO5</td>
<td>11p13-p12</td>
</tr>
<tr>
<td>2M</td>
<td>Fukutin</td>
<td>FKTN</td>
<td>9q31</td>
</tr>
<tr>
<td>2N</td>
<td>O-mannosyltransferase-2</td>
<td>POMT2</td>
<td>14q24</td>
</tr>
<tr>
<td>2O</td>
<td>O-mannose-β1,2-N-acetyl-glucosaminyl transferase</td>
<td>POMGnT1</td>
<td>1p32</td>
</tr>
<tr>
<td>2P</td>
<td>α-Dystroglycan</td>
<td>DAG1</td>
<td>3p21</td>
</tr>
</tbody>
</table>

LGMD = limb-girdle muscular dystrophy
Current treatment remains supportive. Physical therapy enhances functional independence by augmenting range of motion and minimizing contractures. Monitoring cardiac involvement with cardiology consultations, electrocardiography, and echocardiography potentially saves lives. For symptomatic patients, cardiac pacemakers, defibrillators, and transplantation should be considered early in the clinical course.

**LGMD1C—Caveolin-3**

Caveolin-3 gene mutations also produce multiple phenotypes. These include the skeletal myopathies, LGMD1C, LGMD rippling muscle disease (RMD), asymptomatic hyperCKemia, and distal myopathy. External ophthalmoparesis has been reported in conjunction with weakness in caveolinopathy patients. Finally, autosomal recessive inheritance does occur as a patient with homozygous splice-site mutations displayed a mild LGMD phenotype. Within families, individuals bearing identical mutations may manifest differing skeletal muscle phenotypes. Mutations in the gene for caveolin-3 also underlie three cardiac conditions: a hypertrophic cardiomyopathy, a long Q-T syndrome, and a sudden infant death syndrome, both of the latter due to persistent late sodium currents.

Caveolae are 50-100 nm vesicular invaginations in the plasma membrane, thought to participate in vesicular trafficking events and signal transduction processes. Caveolins are integral membrane proteins and the major components of caveolar membranes. Caveolin-3 inhibits dysferlin endocytosis causing its retention at the sarcolemma. Mutant caveolin-3 thus fails to maintain dysferlin in its vigilant posture at the membrane for repair.

<table>
<thead>
<tr>
<th>LGMD</th>
<th>Age at onset (in years)</th>
<th>Clinical pearl</th>
<th>Early distal involvement</th>
<th>Cardiac involvement</th>
<th>Creatine kinase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>20-40</td>
<td>Dysarthria</td>
<td>Sometimes</td>
<td>No</td>
<td>NL-10×</td>
</tr>
<tr>
<td>1B</td>
<td>&lt;10</td>
<td>Joint contractures</td>
<td>Sometimes</td>
<td>Yes</td>
<td>NL-20×</td>
</tr>
<tr>
<td>1C</td>
<td>5-25</td>
<td>Mounding/rippling</td>
<td>Reported</td>
<td>No</td>
<td>2-25×</td>
</tr>
<tr>
<td>1D</td>
<td>15-50</td>
<td>Cardiomyopathy</td>
<td>No</td>
<td>Yes</td>
<td>NL-4×</td>
</tr>
<tr>
<td>1E</td>
<td>30-50</td>
<td>—</td>
<td>No</td>
<td>No</td>
<td>NL-10×</td>
</tr>
<tr>
<td>1F</td>
<td>&lt;15 and &gt;20</td>
<td>Anticipation</td>
<td>No</td>
<td>No</td>
<td>NL-15×</td>
</tr>
<tr>
<td>1G</td>
<td>30-47</td>
<td>Finger flexion limitation</td>
<td>Yes</td>
<td>No</td>
<td>NL-10×</td>
</tr>
<tr>
<td>1H</td>
<td>16-50</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>NL-10×</td>
</tr>
<tr>
<td>2A</td>
<td>5-40</td>
<td>Adductor weakness</td>
<td>No</td>
<td>No</td>
<td>NL-50×</td>
</tr>
<tr>
<td>2B</td>
<td>10-30</td>
<td>Distal leg involvement</td>
<td>Yes</td>
<td>No</td>
<td>2-150×</td>
</tr>
<tr>
<td>2C-F</td>
<td>3-20</td>
<td>“Duchenne”-like</td>
<td>No</td>
<td>Yes</td>
<td>5-120×</td>
</tr>
<tr>
<td>2G</td>
<td>2-15</td>
<td>Brazilian</td>
<td>Yes</td>
<td>Yes</td>
<td>2-30×</td>
</tr>
<tr>
<td>2H</td>
<td>5-30</td>
<td>Hutterite</td>
<td>No</td>
<td>No</td>
<td>NL-20×</td>
</tr>
<tr>
<td>2I</td>
<td>1-40</td>
<td>Respiratory dysfunction</td>
<td>No</td>
<td>Yes</td>
<td>3-50×</td>
</tr>
<tr>
<td>2J</td>
<td>5-20</td>
<td>Finnish</td>
<td>No</td>
<td>No</td>
<td>NL-4×</td>
</tr>
<tr>
<td>2K</td>
<td>&lt;5</td>
<td>Mental retardation</td>
<td>No</td>
<td>No</td>
<td>20-40×</td>
</tr>
<tr>
<td>2L</td>
<td>10-50</td>
<td>Thigh involvement</td>
<td>Sometime</td>
<td>No</td>
<td>NL-50×</td>
</tr>
<tr>
<td>2M</td>
<td>&lt;5</td>
<td>Steroid responsive</td>
<td>No</td>
<td>Yes</td>
<td>5-30×</td>
</tr>
<tr>
<td>2N</td>
<td>&lt;2</td>
<td>MEB traits</td>
<td>No</td>
<td>No</td>
<td>20-30×</td>
</tr>
<tr>
<td>2O</td>
<td>12</td>
<td>MEB traits</td>
<td>No</td>
<td>No</td>
<td>20-50×</td>
</tr>
<tr>
<td>2P</td>
<td>3</td>
<td>Mental retardation</td>
<td>No</td>
<td>No</td>
<td>20×</td>
</tr>
</tbody>
</table>

LGMD1C patients make up between 2-5% of LGMD patients and generally develop symptoms in the first decade. Mild to moderate proximal muscle weakness, muscle cramps, and calf hypertrophy occur. Adults often employ Gower’s maneuver to rise from the floor. Serum CK levels range from 4-25 fold. Muscle histology reveals mildly dystrophic features with fiber size variability, increased connective tissue, and necrotic fibers. Membrane immunostaining with antibodies to caveolin-3 is absent or partially reduced. A vast reduction in caveolae and striking disorganization of the T-tubule system in mice and in humans are revealed by electron microscopy. Molecular diagnosis by gene sequencing is commercially available. Specific treatment is not available.

Mechanically-induced involuntary contractions are the clinical hallmark in RMD. Electrically silent, self-propagating, rolling or “rippling” of muscles can be elicited by passive stretch or tapping of muscles. Localized mounding and rapid contraction of muscle classically are brought on by a knock or a blow to the muscle. Identical CAV3 mutations may lead to LGMD and RMD within the same family.

**LGMD1D-H**

The protein products are not yet determined for the LGMD1D-H autosomal dominant subtypes. LGMD1D is associated with dilated cardiomyopathy and conduction defects, and it maps to chromosome 6q23.9. LGMD1E lacks distinctive features and localizes to 7q.10 Mapped to 7q32.1-32.2, LGMD1F patients’ weakness predominates in the pelvic and shoulder-girdle muscles.11 Interestingly, symptom onset in successive generations...
commences at earlier ages, suggesting genetic anticipation. LGMD1G localizes to 4p21, has onset of proximal weakness between 30 to 47 years of age, progresses slowly, and has the distinctive feature of progressive limitation of finger and toe flexion. Bisceglia and colleagues reported LGMD1H in a 12-member extended family with onset of lower extremity weakness in the teens through the fifth decade. They exhibited a slowly progressive proximal weakness, reduced deep tendon reflexes, proximal muscle atrophy, and calf hypertrophy. A genome-wide screen narrowed the locus to 3p23-p25.

**AUTOSOMAL RECESSIVE LIMB GIRDLE MUSCULAR DYSTrophy**

Autosomal recessive LGMDs are more prevalent and possess higher CK levels (Tables 1 and 2).

**LGMD2A—Calpain-3**

The most common LGMD subtype in many geographic regions, LGMD2A is estimated to represent 9-40% of all cases. Fardeau and colleagues described the clinical, histological, and genetic features in a large, geographically isolated, inbred population on Réunion Island and mapped the chromosomal locus to chromosome 15. The gene encoding the muscle-specific, calcium-activated neutral protease, calpain-3, harbors mutations in this disease.

Clinical onset ranges widely (2-53 years), most often in later childhood or young adulthood. Hyperlordosis and a waddling gait are common. Proximal lower extremity muscles are weaker than shoulder-girdle muscles from the outset. Hip extensor and adductor muscles often display disproportionately severe weakness compared to their respective abductor muscles. Facial muscles may be weak in early onset, severe disease, but oculomotor and velopharyngeal muscles are uniformly spared. Clinical respiratory and cardiac dysfunction seldom impact patients. Common are abdominal laxity and scapular winging, as are hip, knee, and elbow contractures after loss of ambulation. Disease progresses steadily with most patients no longer ambulatory 1-2 decades into their disease. Later onset of disease follows a milder course.

Laboratory evaluation reveals mean CK levels elevated 20 fold with a range of 2-110 times the upper level of normal. Needle EMG yields abnormalities compatible with a myopathy. Variation in fiber size and internal nuclei, increased endomysial connective tissue, and necrotic and regenerating fibers (without inflammatory cells) are features of muscle biopsies. Numerous lobulated fibers may be revealed on oxidative enzyme stains.

The diffuse localization of calpain-3 throughout the muscle fiber essentially precludes diagnosis by immunostaining of muscle. Western blot analysis of muscle demonstrates severely reduced or absent calpain-3 in 80% of cases, but cases with missense mutations may appear normal. Thus, mutation analysis is the diagnostic procedure of choice.

The underlying pathogenic mechanism is not fully understood. Bound to the giant sarcomeric protein, titin, calpain-3 additionally sits poised within the contractile apparatus as part of the mechanism for detection, repair, and turnover of the sarcomere, an integral component in the maintenance of muscle fibers.

No disease specific treatment is available for calpainopathies. However, one 11-year-old girl with LGMD2A presented with eosinophilic myositis and improved on immunosuppressive medications.

**LGMD2B—Dysferlin**

LGMD and distal myopathy may coexist in large, inbred families as the allelic, autosomal recessive disorders LGMD2B and Miyoshi myopathy (MM). Both colocize to chromosome 2p. Mutations in the dysferlin gene (DYSF) were discovered in both LGMD2B and MM, and identical mutations can account for either phenotype. Several cases of symptomatic dysferlin gene carriers, with but a single mutation on one chromosome, have now been reported. Dysferlin, a protein in the ferlin family, plays an important role in membrane trafficking, fusion, and, most notably, repair.

Mutations in DYSF account for 5-35% of LGMD diagnoses and tend to be more prevalent in the regions surrounding the Mediterranean Sea. Dysferlinopathies present with numerous, often overlapping phenotypes: LGMD2B with proximal weakness; MM with distal leg weakness of calf muscles, early involvement of the anterior compartment muscles of the lower legs, a proximodistal pattern, biceps atrophy with deltoid hypertrophy, the combination of calf and deltoid hypertrophy, rigid-spine syndrome, and pseudometabolic and asymptomatic hyperCKemia. Onset generally occurs between 15-30 years of age, although congenital cases and symptomatic onset in the 70s have been reported. Patients develop normally in cognitive and motor spheres, some actually being quite gifted athletically when young. Weakness begins in the legs in nearly all cases, the initial site of involvement determining the nomenclature. Cardiac and respiratory compromise does not occur.

Dysferlinopathies share similar laboratory features. Across the spectrum of clinical presentation, serum CK levels may be substantially elevated, as great as 150 fold. Needle EMG frequently shows small, brief motor units with early recruitment. However, long duration, polyphasic motor units with decreased recruitment often pop up in weak calf muscles. Although divergent in clinical phenotype at onset, lower limb magnetic resonance imaging (MRI) scans reveal similar involvement in both the thighs and forelegs in MM and LGMD2B, and the rate of progression, prognosis, and MRI findings for dysferlinopathies are comparable for both throughout the disease course. The spectrum of muscle biopsy findings vary from slight variability in fiber size and a mild increase in endomysial connective tissue in mildly weak muscles to a few islands of muscle fibers interspersed among widespread fibrous and fatty replacement in atrophic gastrocnemius muscles. Vacuoles are a relatively minor feature, and β-amyloid may be seen with certain mutations but not in most cases. In some series, endomysial and perivascular inflammation are seen in 50% of biopsies. This inflammation has led to misdiagnosis of dysferlinopathies as treatment refractory polymyositis. Ultrastructurally, electron microscopy reveals small
plasmalemmal defects, thickened basal lamina over these defects, replacement of plasma membrane by layers of small vesicles, papillary projections, and tiny subsarcolemmal vacuoles.

Diagnosis may be suspected clinically and on biopsy, but it requires genetic confirmation. Although the very large size of the dysferlin gene (55 exons; >230,000 base pairs and 6,243 coding base pairs; and 2,080 amino acids) makes genetic analysis laborious, genetic testing is commercially available and is the confirmatory and diagnostic procedure of choice. Supportive treatment remains the mainstay.

**LGMD2C-F—Sarcoglycans (γ, α, β, and δ)**

Four sarcoglycans (γ, α, β, and δ) form a heterotetrameric complex spanning the sarcolemma in association with sarcospan, dystrophin, and the dystroglycans. This dystrophin–glycoprotein complex (DGC) provides a mechanical bridge between the extracellular basement membrane, the cytoskeleton, and the intracellular contractile mechanism of myocytes. Additionally, the DGC facilitates cell signaling and trafficking in concert with neuronal nitric oxide synthase, dystrobrevin, and caveolin-3. Muscular dystrophies due to mutations in the different sarcoglycan subunits yield similar clinical and laboratory characteristics. The first sarcoglycan gene locus discovered was γ-sarcoglycan and is thus labeled LGMD2C. LGMD2D, 2E, and 2F correspond to α-, β- and δ-sarcoglycan, respectively.

Highly prevalent in some North African and Brazilian populations, sarcoglycanopathies comprise 10-20% of LGMD cases. Symptoms usually begin between 1-15 years of age. Weakness starts in the pelvic girdle with shoulder-girdle involvement following a few years later. Common examination features include calf hypertrophy, scapular winging, macroglossia, and lumbar hyperlordosis. Many patients are wheelchair dependent within 10 years. Most patients’ disease course mirrors a severe, Duchenne-like progression. Milder cases with slower progression (some with only exercise intolerance, myoglobinuria, or minimal muscle weakness) also occur. Additionally, a case of eosinophilic myositis was recently revealed to be due to mutations of γ-sarcoglycan.

Cardiac and respiratory dysfunction frequently afflict patients. Symptomatic respiratory dysfunction along with arrhythmogenic, dilated, or hypertrophic cardiomyopathies are detected in one-third of patients 10 years into disease.

Serum CK values range from 5-120 times normal. Muscle biopsies show variability in fiber size, central nuclei, degenerating and regenerating fibers, and increased connective tissue infiltration, most often with normal immunostaining for dystrophin. Abnormal staining for all four skeletal muscle sarcoglycans occurs with mutations in any one particular sarcoglycan, and generally the staining pattern cannot be used to predict the genotype. Genetic testing is commercially available for the four sarcoglycan genes. Treatment requires attention to cardiac, respiratory, and orthopedic complications. Similar to dystrophinopathies, treatment with deflazacort stabilized and improved strength over a 22-month period in two siblings with LGMD2E. A number of other molecular therapies are on the horizon.

**LGMD2G—Telethonin**

A member of the Z-disc of skeletal and cardiac muscle along with titin, α-actinin, and myotilin, telethonin serves as a substrate for titin, which phosphorylates the carboxy-terminal region of telethonin in early differentiating myocytes. The gene for telethonin (TCAP) on chromosome 17q11-12 harbors mutations in LGMD2G.

Clinically, disease begins before age 15 years, initially degrading walking, running, and stair climbing. Weakness predominates in the proximal upper extremities and in both the proximal and the distal lower extremities. Ankle dorsiflexor weakness leads to heel walking difficulties and later foot drop. Despite the fact that TCAP mutations cause a hereditary dilated cardiomyopathy, cardiac disease arises infrequently. Wheelchair confinement ensues prior to the fifth decade. Most cases have been reported in Brazil.

Serum CK levels, elevated 3-17 fold at onset, decline to nearly normal in wheelchair-dependent patients. Muscle biopsy histology reveals variability in fiber size, necrotic and regenerating fibers, central nuclei, and excess endomysial connective tissue. Rimmed vacuoles abound. In LGMD2G patients, anti-telethonin antibody immunostaining is absent from the sarcoplasm but present in nuclei.

Gene sequencing is commercially available at this time, and treatment remains supportive.

**LGMD2H—TRIM 32**

A mild, autosomal recessive, LGMD affects Manitoba Hutterites. In LGMD2H, slowly progressive weakness and muscle loss ensues after disease onset in the first decade. Initially confined to the quadriceps and the pelvic girdle, strength in the proximal upper extremities, brachioradialis, and anterior tibial muscles later declines. Preferential involvement of the trapezius and deltoid muscles, with sparing of the pectoralis muscles, leads to a “peculiar inward shrugging” posture. Facial muscles mildly sag, but cardiac and intellectual function is preserved. Patients poorly arise from the floor or low chairs, but they remain ambulatory into their 30s.

Serum CK ranges up to 12 times normal. Needle EMG yields a nonirritable myopathy. Muscle biopsies show increased variability in fiber size, fibers with central nuclei, fatty and connective tissue replacement, and occasional fibers with vacuoles.

Mutations at chromosome 9q31-33 in the gene TRIM32, a member of the family of tripartite-motif (TRIM) proteins, cause LGMD2H21 as well as sarcotubular myopathy. These mutations also underlie some cases of Bardet-Biedl syndrome. Gene sequencing is commercially available.

**LGMD2I—Fukutin-Related Protein**

Initially described in a large Tunisian family, LGMD2I is mapped to chromosome 19q13.3. Mutations in the FKRP gene at that locus were discovered in congenital muscular dystrophy 1C, in milder patients with later onset (LGMD2I), in asymptomatic hyperCKemia, and in isolated dilated cardiomyopathy.
Clinically, symptoms develop over a broad age range, from 1-50 years, but on average in the second decade of life. LGMD2I likely comprises 10-15% of LGMD cases in North America. Prominent respiratory and cardiac dysfunction may arise early in the clinical course and may not correlate with skeletal muscle involvement. Initial pellviemoral weakness subsequently spreads to the distal lower extremities and proximal upper extremities. Calf hypertrophy and lumbar lordosis are nearly universally present. Scapular winging, cognitive dysfunction, and MRI abnormalities may be seen in some cases. Identical FKRP mutations may cause muscle disease of either congenital or early adult onset within the same family.

Forced vital capacity may be reduced by 50% or more, especially when measured in a supine position. Echocardiograms demonstrate left ventricular dysfunction, while electrocardiograms and Holter monitors evaluate for arrhythmias. Cardiovascular MRI is more sensitive than conventional cardiac diagnostic investigations and may detect abnormalities (both symptomatic and presymptomatic) in the majority of patients. The extent of cardiac muscle involvement can be quite disparate from that in skeletal muscles. Serum CK ranges from 3-50 times normal. Muscle biopsies show fiber size variation, fiber splitting, central nuclei, endomysial replacement with fatty and fibrous tissue, and diminished immunostaining for α-dystroglycan. Gene sequencing is commercially available.

Of utmost importance in LGMD2I, monitoring of respiratory and cardiac function should take place in alternate years in asymptomatic patients and more frequently for those with previous testing abnormalities. Respiratory support with noninvasive ventilation and early treatment of cardiac dysfunction with medications, pacemakers, defibrillators, and transplantation improve quality of life. Definitive treatment is not yet available.

**LGMD2J—Titin**

The giant, filamentous protein titin spans half the sarcomere from the Z disc to the M line and contains ligand binding sites for the muscle-specific protease calpain-3 (see LGMD2A above). Heterozygous mutations (autosomal dominant inheritance) of the gene for titin (TTN) underlie LGMD2J, a distal Miyoshi myopathy (MMD3), and, in some cases, asymptomatic hyperCKemia. Similar to dysferlin and caveolin, evidence suggests anoctamin plays a role in sarcolemmal maintenance and repair. Onset of disease occurs from 11-55 years of age with some requiring wheelchair use after 10-15 years. Proximal lower extremity muscles are affected earliest, though inability to walk on the toes often ensues. CK levels range from normal to elevated 50 fold (average = 4,500 IU/L). Muscle MRI reveals pronounced and asymmetric atrophy of the biceps brachii in the upper extremities and the medial quadriceps femoris hamstring and adductor magnus muscles. Anoctaminopathy likely represents a common cause of adults on set muscular dystrophy with high serum CK values. Genetic testing is commercially available.

**CURRENT AND FUTURE DIRECTIONS**

LGMDs pose diagnostic and treatment challenges for the clinician. Many university based neuromuscular groups now are adept at immunohistochemical evaluation of muscle biopsies. Panels for reflexive sequencing of genes involved in the adult muscular dystrophies are available and cover LGMDs 1B, 1C, 2A, 2B, 2C-F, and 2I. These panels will derive a diagnosis in 60-80% of patients with LGMD. It is imperative to remember the much higher prevalence of dystrophinopathies and facioscapulohumeral muscular dystrophy when evaluating patients with progressive muscle weakness. The speed of mutation analysis is increasing in logarithmic fashion, and the age of whole genome sequencing may arise early, though inability to walk on the toes often ensues. CK levels range from normal to elevated 50 fold (average = 4,500 IU/L). Muscle MRI reveals pronounced and asymmetric atrophy of the biceps brachii in the upper extremities and the medial quadriceps femoris hamstring and adductor magnus muscles. Anoctaminopathy likely represents a common cause of adults onset muscular dystrophy with high serum CK values. Genetic testing is commercially available.
cardiomyopathies. Promising genetic manipulation strategies are underway in clinical trials. Unwavering commitment to discovering effective interventions to slow or halt disease progression, reverse or prevent the disease mechanism, and repair already damaged tissue should one day fulfill these patients’ dreams of a cure.29

REFERENCES

CASE ONE

Presentation

A 62-year-old male presents with a history of a seizure disorder, macular degeneration, bilateral cataracts, cardiac arrhythmia (after defibrillator placement), and a cardiomyopathy. He complains of 3 years of leg weakness (right greater than left) with difficulty climbing stairs and arising from sitting. He reports these symptoms have plateaued. He denies any upper extremity weakness, cramps/muscle twitches, numbness/tingling anywhere, neck pain, low back pain, shortness of breath, or any difficulty with swallowing and chewing. He reports a normal childhood in which he was able to keep up with all his sibling and peers. There was no complication during his birth. Within the last year, he began to use a straight cane due to occasional falling and tripping.

Ten years ago, he was participating in 10 K road races. He began to experience frequent atrial flutter that required an ablation 5 years earlier. Cardiovascular imaging revealed severe right ventricular enlargement and systolic dysfunction. An invasive electrophysiology study is notable for inducibility of ventricular tachyarrhythmias and he had placement of an implantable cardioverter-defibrillator 2 years earlier.

Previous Workup

The patient had a computed tomography myelogram of the cervical, thoracic and lumbar spine 2 years ago. It revealed no significant spinal canal stenosis. There were minimal degenerative changes in the cervical and lumbar spine, as described in the examination results (below). There was marked bilateral atrophy of the psoas muscles and of the paraspinal muscles at the level of the thoracic spine (of uncertain etiology) but it may be related to patient’s reported lower extremity weakness, requiring clinical correlation.

The patient underwent a right ventricular endomyocardial biopsy nearly 4 years ago. It revealed moderate-to-severe myocyte hypertrophy. Interstitial and perivascular fibrosis was moderate. Replacement fibrosis was consistent with a healed ischemic injury. There was diffuse fibrous endocardial thickening. There was no evidence of active myocarditis, acute or recent myocardial infarction, amyloid heart disease, granulomatous disease, or iron deposition. There is insufficient adipose tissue to make a diagnosis of arrhythmogenic right ventricular cardiomyopathy.

History and Medications

Past Medical History: The patient has a cardiac arrhythmia and cardiomyopathy, with right atrial and ventricular dilatation (after his defibrillator was implanted). He was diagnosed with a seizure disorder at age 18; the last episode (complex partial) was about 10 years ago. He is legally blind with macular degeneration for about 30 years. He has bilateral cataracts and suffers from migraines. He has hearing loss, which was diagnosed earlier this year.

Family History: The patient’s sister died in her 40s, and it was thought to be related to complications of obesity and diabetes. His mother had epilepsy and died after a falling injury. His father died...
due to cirrhosis when he was a child. He has two brothers, a 60-year-old and 55-year-old, both alive and healthy.

**Medications:** Phenytoin 500 mg every bedtime, atenolol 25 mg daily, aspirin 81 mg, and simvastatin (started 1 month ago).

**Physical Examination**

**General Appearance:** The patient is a pleasant male in no apparent distress. Skin: No rash noted.

**Musculoskeletal:** No scoliosis, lordosis, pes cavus, or hammertoes. Kyphosis.

**Neurological Examination**

**Mental Status:** The patient is alert, attentive, and oriented (×3). His speech is coherent and fluent without dysarthria or aphasia. His memory, comprehension and ability to follow commands were intact. He achieved a 3/3 for immediate and 5-min recall of objects. His symptoms do not fluctuate, but the weakness is worse with activity.

**History and Medications**

**Past Medical History:** Otherwise negative.

**Family History:** There is no family history of neuromuscular disease. He has eight healthy siblings.

**Medications:** None.

**Physical Examination**

**Head, Eye, Ear, Nose, and Throat (HEENT):** The face was somewhat narrow and elongated. There was a high arched palate. Skin: No rashes appreciated, no nailbed changes.

**Musculoskeletal:** No scoliosis. There is exaggerated lumbar lordosis. No contractures.

**Neurological Examination**

**Mental Status:** Normal.

**Cranial Nerves II-XII:** Intact.

**Motor Examination:** The patient has normal muscle bulk in the upper extremities and normal tone throughout. There is no evidence of fasciculations. No atrophy or hypertrophy. There is no action or percussion myotonia or paramyotonia. No scapular winging. Manual muscle testing (MMT) revealed Medical Research Council (MRC) grade 5/5 strength throughout, including the proximal and distal muscles of the arms. In the lower extremities, his results showed the following: hip flexors/extensors/abductors 2, knee extensors 5, knee flexors 4, ADF 4+, APF 5. Neck flexors 4, neck extensors 5.

**Coordination:** Complex motor skills revealed normal coordination. Finger-nose-finger was intact.

**Sensory Examination:** Normal.

**Gait:** Patient had a slow, wide base gait. He was not able to walk on his heels and toes.

**Reflexes:** Deep tendon reflexes (DTRs) were 2 at the biceps, triceps, brachioradialis, knees, and ankles. Plantar responses were flexor bilaterally. Hoffman’s sign was positive bilaterally.

**CASE TWO**

**Presentation**

A 44-year-old man presents with a history of weakness that he first appreciated 2 years ago that began as neck extensor weakness and then progressed to involve proximal limb muscles. Over the next few months the weakness gradually spread to involve his shoulders. He began to have difficulty washing his hair or using his arms overhead. He then developed leg weakness. He has no blurred or double vision, ptosis, dysarthria, dysphagia, dyspnea, cramps, myalgias, fasciculations, numbness, or parasthesias.

Needle Electromyography (EMG): Needle EMG revealed early recruitment of short duration, small amplitude, polyphasic motor unit action potentials in proximal extremity muscles without abnormal spontaneous activity. Fibrillations, positive sharp waves, and pseudomyotonic discharges were seen in the paraspinal muscles.

**Laboratory Results:** Serum creatine kinase (CK) was elevated at 1,017 IU/L.
CASE THREE

Presentation

A 79-year-old right-handed woman is referred for muscle weakness and aches primarily involving her arms and shoulders that began 1-1/2 years after starting atorvastatin (Lipitor®). The Lipitor® dose was decreased; however, followup blood tests with aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were elevated, so the decision was made to discontinue the medication. However, her weakness continued to progress over the next year. She denies weight loss, shortness of breath, swallowing difficulty, arthralgias, or rash.

History and Medications

Past Medical History: The patient has hypertension, atrial fibrillations, dyslipidemia, and macular degeneration. She underwent a hysterectomy for uterine cancer 13 years ago and has since been in remission.

Family History: There is no family history of neuromuscular diseases. All four of her siblings and her mother have diabetes. One sister underwent coronary artery bypass graft surgery. The patient has six children, three boys and three girls, all healthy.

Social History: Patient lives with her daughter. She is a retired nurses assistant. She denies history of smoking, alcohol, or drug abuse.

Medications: Coumadin, lisinopril, amlodipine (Norvasc®), and multivitamin.

Physical Examination

Skin: The patient was noted to have mild redness involving her forehead, cheeks, and nose. No other skin lesions noticed as well as no Gottron’s papules or nailbed changes.

Musculoskeletal: No scoliosis, lordosis, kyphosis, pes cavus, or hammertoes.

Neurological Examination

Mental Status: Intact.

Cranial Nerves II-XII: Intact.

Motor Examination: The patient has normal muscle bulk and tone. There is no evidence of atrophy or fasciculations. There is no action or percussion myotonia or paramyotonia. MMT revealed the following MRC grades (right/left): shoulder abduction and shoulder flexion 4−/4−, elbow flexion and elbow extension 4/4, wrist extension and wrist flexion 5/5, abductor pollicis brevis and first dorsal interosseous 5/5, abductor digiti minimi and abductor pollicis longus 5/5, hip flexion sitting 4−/4 and lying down 3/4−, hip abduction 3−/4−, knee extension 5/5, knee flexion 4+/4+, hip extension 4/4, foot dorsiflexion and plantar flexion 5/5, neck flexion 4−, and neck extension 4. The patient was not able to stand up from a sitting position.

Coordination: Complex motor skills revealed normal coordination. Finger-to-nose and heel-to-shin were intact.

Sensory Examination: The patient was revealed to have normal vibratory, pinprick, light touch, and proprioception bilaterally. Romberg’s test was negative.

Gait: The patient was able to walk on her heels, toes and tandem without any difficulty.

Reflexes: DTRs were 2 at the biceps, triceps, brachioradialis, knees, and ankles bilaterally. Plantar responses were flexor bilaterally.

Laboratory Results: Serum CK was 1,974 IU/L.

CASE FOUR

Presentation

A 66-year-old woman presents with a gradual onset of weakness over the past 30 years. Weakness began in earnest 9 years ago when she fell. Serum CK ranged between 600 and 3,000 IU/L. She had an outside needle EMG which demonstrated myopathic features. An outside muscle biopsy of the left biceps also showed myopathic features and inflammation. She was treated with steroids and methotrexate with little benefit and her weakness continued to worsen. These medications were stopped and she was referred for a second opinion.

She has difficulty lifting her arms to her head and she has difficulty with her legs in getting in and out of chairs and climbing stairs. She denies myalgias, cramps, history of myoglobinuria, fasciculations, muscle stiffness, or difficulty in relaxing the muscles. She has no numbness or paresthesia. She chews and swallows food/liquids without difficulty. There has been no visual or speech problem. She has no shortness of breath, palpitations, or episodes of near syncpe. She has had no difficulty with bladder or bowel control.

History and Medications

Past Medical History: The patient has polymyositis, degenerative joint disease, gastroesophageal reflux disease (GERD), and hypertension. She underwent a thyroidectomy due to nodules.

Family History: There is no family history of a neuromuscular disorder.

Social History: She does not smoke or drink.

Medications: Levothyroxine (Levoxyl®), irbesartan (Avapro®), citalopram (Celexa®), hydrochlorothiazide and triamterene (Dyazide®, diltiazem (Cartia®), omeprazole (Prilosec®), prednisone 5 mg daily, tolterodine (Detrol®), celecoxib (Celebrex®), clonazepam (Klonopin®), ranitidine (Zantac®), raloxifene (Evista®), creatine, vitamin C, vitamin E, multivitamin, aspirin, and calcium.

Physical Examination

General: This is a well-nourished, well-developed woman in no distress.
Skin: There is no rash to suggest dermatomyositis.

Musculoskeletal: There is no pes cavus or hammertoe deformity.

Neurological Examination

Mental Status: The patient is awake and oriented (×3) with normal language, praxis, memory, and attention.

Cranial Nerves: The visual fields are full. The fundi are normal appearing. The pupils are round and react to light and accommodate. There is no ptosis. There is no nystagmus. Extraocular movements are normal. Facial strength is normal. Facial sensation is normal. Hearing is normal. Neck flexion and extension strength are normal.

Motor Examination: The patient has winging of both scapula. There is no focal muscle atrophy or hypertrophy evident. No myotonia, paramyotonia, rippling muscles, or fasciculations were observed. MMT revealed 3/5 strength in the deltoids, 4/5 biceps, 5−/5 triceps, 5/5 distally in the legs. Hip flexors are 4+/5; quadriceps, tibialis anterior, and gastrocnemius 5/5.

Sensory Examination: Light touch, cold, vibration, and proprioception are normal throughout. Romberg’s sign is absent. Coordination: Finger-to-nose and heel-to-shin testing are unremarkable.

Reflexes: Absent throughout. Plantar responses are flexor bilaterally.

Gait: She has a wide-based, wobbling gait and a hyperlordotic posture. She can walk on her toes but not her heels.

CASE FIVE

Presentation

A 78-year-old woman presents with muscle weakness since she was at least 35 years of age. She met all her early motor milestones. However, she states that even as a young child she was not very athletic and noted that she had difficulty keeping up with the other kids and that she could not run as fast as the other kids. She would get short of breath when doing physical activities as a young child. She also noted some difficulty swallowing as a young child as well.

Around age 35, she began to develop proximal weakness in that she had trouble going upstairs or getting out of a chair and difficulty lifting. She continued to have progressive difficulty walking and started using a cane about 7 years ago and more recently over the last 2-3 years has been using a walker. Around 2000 (age 72 years), she was diagnosed with hyperparathyroidism when a lump in her throat was discovered and she was found to have osteoporosis of her arms. She states that at that time she was very tired and had no energy. She underwent a parathyroidectomy and over the following 6-7 months her fatigue improved somewhat. However, over the past several years her strength has continued to worsen and she has less stamina.

Currently, she has difficulty with stairs and washing her hair. She denies any muscle stiffness, twitches, or myalgias. She also has had progressive dysarthria and dysphagia, which has progressed over the last year. She states that she chokes on her saliva. She also has difficulty swallowing cereals and pudding. She feels that she tires while eating, but denies any regurgitation. She has occasional shortness of breath with activity. She has been recently diagnosed with hypoventilation and requires oxygen at night. She denies any morning headaches or difficulty, but she does have difficulty sleeping secondary to knee pain. She denies any numbness, tingling, or significant bowel or bladder dysfunction. She has no complaints of muscle atrophy, cramps, or fasciculations.

Previous Workup

Laboratory testing has included a normal serum CK (100 IU/L), AST, and ALT. Most recent thyroid stimulating hormone and parathyroid levels were both normal. Antinuclear antibodies were elevated at 1:320 in a speckled pattern. Anti-Ro was elevated but anti-double stranded DNA, anti-ribonucleoprotein, anti-Jo-1, and anti-Scl70 were all negative. Rheumatoid factor was 111. She had a needle EMG/nerve conduction study performed elsewhere that was interpreted as showing myopathic features in the iliopsoas muscles. There were also “denervation” changes in the lower extremities, which were interpreted as consistent with superimposed L2-S1 radiculopathies. The patient also underwent a muscle biopsy of the left quadriceps 10 years ago. This was significant for increased variation in fiber size with rare atrophic fibers and type II fiber atrophy.

History and Medications

Past Medical History: The patient has hypertension, hypercholesterolemia, osteoporosis, glaucoma, medication-induced hepatitis, a history of hyperparathyroidism, and hyperthyroidism (now hypothyroid post-treatment).

Past Surgical History: The patient has undergone gallbladder, tonsillectomy, appendectomy, uterine and bladder surgery, cataract excision, parathyroidectomy, and thyroidectomy.

Family History: There is no history of neuromuscular disease.

Medications: Latanoprost (Xalatan®) eyedrops, diltiazem, fenofibrate (Tricor®), hydrochlorothiazide, levothyroxine (Levoxy®), candesartan (Atacand®), aspirin, vitamin D, calcium, and multivitamin.

Physical Examination

Skin: No rashes were noted.

Musculoskeletal: No abnormalities were noted.

Neurological Examination

Mental Status: Intact.

Cranial Nerves: Extraocular movements intact. There was no face or jaw weakness. There was marked tongue weakness; it was
unable to protrude but there were no atrophy or fasciculations (if anything there was macroglossia). The palate elevated symmetrically. Shoulder shrug was normal.

**Motor Examination:** The patient was revealed to have normal muscle bulk and tone. There was no evidence of atrophy or fasciculations. There was no action or percussion myotonia or paramyotonia. MMT revealed MRC grades as follows: 5−/5 upper extremities weakness of the deltoids bilaterally, 4/5 weakness of the biceps bilaterally. The rest of the muscles in the arms were 5/5 bilaterally. In the lower extremities, she had 2/5 weakness of the hip flexion on the left and 3/5 on the right; hip abductors were 4/5; knee extensors, flexors, and foot flexion and extension and toe flexion and extension were 5/5 bilaterally. The patient was able to stand her toes, but unable to stand on her heels.

**Coordination:** Complex motor skills revealed normal coordination.

**Sensory Examination:** Intact.

**Gait:** The patient had a wide-based, waddling gait and required the use of a walker. She was unable to rise from a chair without help.

**Reflexes:** DTRs were 2+ in the upper extremities and unelicitable in the lower extremities. Plantar responses are flexor bilaterally.

**CASE SIX**

**Presentation**

A 71-year-old right-handed white female presents with a 10-year history of difficulty climbing stairs and arising from chairs. She denies any weakness in her arms. Rarely, she has some swallowing difficulties. She denies any ptosis or double vision, shortness of breath, numbness or tingling, muscle pain, or tenderness.

She has had mildly elevated serum CK in the 200 IU/L range. She had a needle EMG of a leg, which apparently showed some myopathic units in her tibialis anterior. There was no evidence of abnormal insertional or spontaneous activity. She had a magnetic resonance imaging scan of the lumbosacral spine which was unremarkable.

She has had mildly elevated serum CK in the 200 IU/L range. She had a needle EMG of a leg, which apparently showed some myopathic units in her tibialis anterior. There was no evidence of abnormal insertional or spontaneous activity. She had a magnetic resonance imaging scan of the lumbosacral spine which was unremarkable.

She underwent a biopsy of the left quadriceps muscle 3 years ago, which showed chronic granulomatous inflammation with numerous multinucleated giant cells. There was variability and muscle fiber size. She had a chest x-ray, which showed some bilateral upper lobe scarring, but no enlarged mediastinal nodes. Tuberculosis skin test was negative. Her pulmonary function tests were normal. She did have a mildly elevated angiotensin-converting enzyme level of 65.

She was started on prednisone 60 mg/day for a month, followed by 50 mg/day for a month, 40 mg/day for a month, 30 mg/day for a month, 20 mg/day for a month, and then was put on 10 mg/day every other day. She thought that perhaps initially she had increased strength in her trunk (she was able to lift better with her back muscles on prednisone). Otherwise, she has noticed no significant improvement in her strength on the prednisone. So, she was started on azathioprine.

Most recent laboratory results showed a serum CK which was normal at 158 IU/L.

**History and Medications**

**Past Medical History:** The patient’s past medical history is otherwise remarkable for hypertension and GERD. She also said that in the past she had hepatitis of unclear etiology.

**Family History:** Remarkable for a son with rheumatoid arthritis.

**Medications:** Prednisone 10 mg/day, azathioprine 50 mg/day, hydrochlorothiazide 25 mg/day, and ranitidine (Zantac®).

**Physical Examination**

**General:** Examination, including skin, was unremarkable.

**Neurological Examination**

**Mental Status:** Intact.

**Cranial Nerves II-XII:** Intact.

**Motor Examination:** The patient was revealed to have atrophy of the volar forearm muscles and quadriceps. MMT revealed the following MRC scores: orbicularis oculi 5, neck flexion 4, neck extension 5, shoulder abduction 4, elbow flexion 4, elbow extension 4+, wrist extension 4, wrist flexion 4+, finger extension 4, finger flexion 4+. In the lower extremities hip flexion, abduction, and extension were 3−, knee extension 5, knee flexion 4−, ankle dorsiflexion 4−, and ankle plantar flexion 5.

**Gait:** The patient had a slightly wide-based waddling gait. She landed with her heels. Her stride was sometimes flatfooted.

**Reflexes:** Normal sensation and DTRs.
Myopathies: Issues in Diagnosis and Treatment

CME Questions

1. All of the following disorders can have muscle stiffness/myotonia EXCEPT:
   A. Myotonic dystrophy type 1.
   B. Myotonic dystrophy type 2.
   C. Paramyotonia congenita.
   D. Hyperkalemic periodic paralysis.
   E. Facioscapulohumeral dystrophy.

2. Asymmetric weakness with predominant involvement of the distal forearm muscles and the knee extensor muscles is typically seen in which of the following disorders?
   A. Dermatomyositis.
   B. Myotonic dystrophy type 1.
   C. Acid-maltase deficiency.
   D. Inclusion body myositis.
   E. Duchenne muscular dystrophy.

3. Which of the following toxins can cause myosin (thick filament) loss myopathy?
   A. High dose intravenous steroids and non-depolarizing neuromuscular blocking agents.
   B. Cholesterol lowering drugs and alcohol.
   C. Chloroquine and colchicine.
   D. Procainamide and l-tryptophan.
   E. Emetine and vincristine.

4. Myopathies associated with cardiac disease include all of the following EXCEPT?
   A. Kearns-Sayre syndrome.
   B. Andersen’s syndrome.
   C. Emery-Dreifuss muscular dystrophy.
   D. Inclusion body myositis.
   E. Acid maltase deficiency.

5. A scapuloperoneal distribution of muscle weakness can occur in all of the conditions except:
   A. Facioscapulohumeral dystrophy.
   B. Acid maltase deficiency.
   C. Emery-Dreifuss dystrophy.
   D. Congenital myopathies.
   E. Hypothyroid myopathy.

6. Immune-mediated necrotizing myopathy is associated with all of the following EXCEPT:
   A. Anti-SRP antibodies.
   B. Statin use.
   C. Distal greater than proximal weakness.
   D. Response to immunosuppression.

7. All of the following are pathognomonic findings for dermatomyositis EXCEPT:
   A. Perivascular inflammation.
   B. Gottron’s sign.
   C. Perifascicular atrophy.
   D. Heliotrope rash.

8. All of the following are typical features of inclusion body myositis EXCEPT:
   A. Dysphagia.
   B. Asymmetric weakness.
   C. Distal weakness.
   D. A small but definite response to prednisone therapy.

9. All of the following are true about treating patients with autoimmune myopathy EXCEPT:
   A. Intravenous immunoglobulin may be considered for use in pregnant patients.
   B. Prednisone therapy should never be tapered until CK levels have normalized.
   C. Subcutaneous administration of methotrexate may minimize its gastrointestinal side effects.
   D. Hydroxychloroquine is sometimes used to treat dermatomyositis, but may cause a toxic myopathy.

10. A wheelchair-confined, 10-year-old male presents with proximal weakness, 20 degree contractures at his elbows, and a creatine kinase (CK) level of 220 U/L. His family history reveals a 30-year-old mother without symptoms and a 53-year-old maternal grandfather with an arrhythmogenic cardiomyopathy since 32 years of age. The most likely limb-girdle muscular dystrophy (LGMD) subtype for this boy is:
    A. LGMD1B – Laminopathy.
    B. LGMD1C – Caveolinopathy.
    C. LGMD2A – Calpainopathy.
    D. LGMD2B – Dysferlinopathy.
11. The autosomal recessive LGMDs are:
A. More prevalent and have higher CK values than the autosomal dominant LGMDs.
B. More prevalent and have lower CK values than the autosomal dominant LGMDs.
C. Less prevalent and have higher CK values than the autosomal dominant LGMDs.
D. Less prevalent and have lower CK values than the autosomal dominant LGMDs.

12. LGMDs 2I, 2K, 2M, 2N, 2O and 2P all act through the same pathophysiologic mechanism, which is:
A. Caveolar disruption with abnormal signal transduction.
B. Inadequate sarcolemmal repair.
C. Disturbance of the dystrophin-glycoprotein complex.
D. Hypoglycosylation of α-dystroglycan.

13. Two 18-year-old siblings, both on the cross country team, noted substantial reductions in their 5 kilometer race times over the past year and now some trouble climbing stairs. Their CK levels were 22,847 U/L and 27,466 U/L, and their muscle biopsies revealed moderate variability in fiber size, mildly increased endomysial connective tissue, collections of endomysial inflammatory cells, and rare vacuoles. The most likely LGMD subtype is:
A. LGMD1A – Myotilinopathy.
B. LGMD1C – Caveolinopathy.
C. LGMD2B – Dysferlinopathy.
D. LGMD2G – Telethoninopathy.

14. All of the following LGMD subtypes may have prominent cardiac involvement EXCEPT:
A. LGMD1B – Laminopathy.
B. LGMD2A – Calpainopathy.
C. LGMD2E – α-sarcoglycanopathy.
D. LGMD2I – FKRP.

15. A mother and her two sons all had onset of proximodistal weakness of the legs, proximal weakness of their arms, and nasal dysarthria in the third decade of life. CK levels were <500 U/L. A biopsy showed Z-band streaming. The LGMD diagnosis in this family is:
A. LGMD1A – Myotilinopathy.
B. LGMD1B – Laminopathy.
C. LGMD1C – Caveolinopathy.
D. LGMD2F – α-sarcoglycanopathy.

16. An ambulatory 27-year-old female with LGMD2C (α-sarcoglycanopathy) and mild skeletal muscle weakness has developed an end-stage cardiomyopathy with a left ventricular ejection fraction of 15%. She has already been treated with ACE inhibitors, beta blockers, implantable pacemaker/defibrillator, and a left ventricular assist device. At the current time, the next step in management would be:
A. Trial on corticosteroids.
B. Trial on an angiotensin receptor blocking agent.
C. Referral for cardiac transplantation.
D. Referral for bone marrow transplantation.

17. Which of the following excludes a diagnosis of late-onset Pompe disease?
A. Normal serum CK level.
B. EMG demonstrated myotonic discharges.
C. Early ventilator muscle failure.
D. Lack of vacuoles and increased glycogen on muscle biopsy.
E. None of the above.

18. Which of the following is characteristic of multiacyl-dehydrogenase deficiency (MADD)?
A. Recurrent bouts of myoglobinuria.
B. Markedly decreased carnitine levels in serum and muscle biopsy.
C. Increased acylcarnitine levels of various carbon lengths and abnormal urine organic acid levels (C5-C10 dicarboxylic aciduria +/- acylglycines).
D. Decreased carnitine palmitoyltransferase 2(CPT2) activity on muscle biopsy.
E. Exercise forearm tests revealed normal rise in lactic acid but no rise in ammonia.

19. Which of the following features is typical of LGMD2A (calpainopathy)?
A. Scapular winging.
B. Prominent hypertrophy of calf muscles.
C. Early ventilatory muscle involvement.
D. Early cardiac muscle involvement.
E. Normal serum CK and needle electromyography (EMG).

20. You are evaluating a patient who carries a diagnosis of polymyositis but has no significant improvement in strength despite being treated with high-dose prednisone (1.5 mg/kg/day) for 4 months. Which of the following would be the most appropriate next step?
A. Add a second-line immunosuppressive agent, such as methotrexate, azathioprine, or mycophenolate mofetil.
B. Add an immunomodulating agent, such as intravenous immunoglobulin.
C. Give a course of rituximab.
D. Pulse the patient with IV methylprednisolone 1 gm daily for 3 days then increase the prednisone to 2.0 gm/kg/day for at least two more months.
E. Examine the patient with particular attention to pattern of muscle weakness and atrophy.
21. A 19-year-old man presents with a 6-month history of weakness in his legs. He describes difficulty climbing stairs and arising from chairs. On clinical examination, he has mild hip girdle weakness (Medical Research Council grade 4+/5); his hamstrings are 4/5; and ankle plantar flexors are 3/5. His knee extensors and ankle dorsiflexors are normal, as are his upper extremity and facial muscles. He has no scapular winging or muscle hypertrophy, though you note atrophy of the medial gastrocnemius muscles bilaterally and he is unable to stand on his tip toes. Sensation is intact. Muscle stretch reflexes are 2/4 and symmetric throughout, except at the ankles where they are absent. His serum CK level is 12,000 U/L. Which of the following would be the most appropriate next step?

A. Order a Western blot for dysferlin analysis on peripheral monocytes or sequencing of the dysferlin gene for mutations.
B. Obtain a dried blood spot analysis for alpha-glucosidase activity, as it would be important not to miss a possible treatable condition (i.e., late-onset Pompe disease).
C. Perform an EMG/NCS.
D. Do a gastrocnemius muscle biopsy, as it is the most severely affected.
E. Treat the patient empirically with prednisone 1.0 to 1.5 mg/kg daily for presumed polymyositis.
Please be aware that some of the medical devices or pharmaceuticals discussed in this handout may not be cleared by the FDA or cleared by the FDA for the specific use described by the authors and are “off-label” (i.e., a use not described on the product’s label). "Off-label" devices or pharmaceuticals may be used if, in the judgment of the treating physician, such use is medically indicated to treat a patient’s condition. Information regarding the FDA clearance status of a particular device or pharmaceutical may be obtained by reading the product’s package labeling, by contacting a sales representative or legal counsel of the manufacturer of the device or pharmaceutical, or by contacting the FDA at 1-800-638-2041.
Crossfires: Piriformis Syndrome, Thoracic Outlet Syndrome, and Tarsal Tunnel Syndrome

Table of Contents

Course Committee 4

Faculty 5

Neurogenic Thoracic Outlet Syndrome is Overdiagnosed: Wilbourn Revisited
Shawn J. Bird, MD 7

Neurogenic Thoracic Outlet Syndrome is Underdiagnosed: The Roos-Wilbourn Debate Revisited
Kaj H. Johansen, MD, PhD 11

Tarsal Tunnel Syndrome: Underdiagnosed
Mohammad A. Saeed, MD and Edgar Steinitz, MD, MS 15

Tarsal Tunnel Syndrome is Overdiagnosed
Michael D. Weiss, MD 21

Piriformis Syndrome and Functional Electromyography
Loren M. Fishman, MD 25

Piriformis Syndrome is Overdiagnosed
Robert Werner, MD, MS 35

CME Questions 39

Dr. Weiss is a speaker for Walgreen’s Infusions and Talecris Biotherapeutics. Any conflict of interest was resolved according to ACCME Standards. All other authors/faculty have nothing to disclose.

Course Chair: Mahammed Saeed, MD, MS

The ideas and opinions expressed in this publication are solely those of the specific authors and do not necessarily represent those of the AANEM.
Objectives

Objectives - This course provides a comprehensive overview of spasticity evaluation and management. Participants will acquire skills to (1) explain the controversies in evaluation, surgical management and new treatment options in neurogenic thoracic outlet syndrome, (2) discuss whether the use of electrodiagnostic studies in tarsal tunnel syndrome is under or over utilized, and (3) describe the pros and cons in the role of electrodiagnostic studies in the evaluation and management of piriformis syndrome.

Target Audience:
• Neurologists, physical medicine and rehabilitation and other physicians* interested in neuromuscular and electrodiagnostic medicine
• Health care professionals involved in the management of patients with neuromuscular diseases
• Researchers who are actively involved in the neuromuscular and/or electrodiagnostic research
Physicians who are eligible to attend the AANEM meeting are MDs, DOs, and overseas equivalents.
Healthcare Professionals and Researchers who are not AANEM members must receive a letter of support from a Fellow AANEM member to attend the meeting.

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 live activity for a maximum of 3.25 AMA PRA Category 1 Credits™. If purchased, the AANEM designates this enduring material for a maximum of 6.25 AMA PRA Category 1 Credits™. 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. Physicians should claim only the credit commensurate with the extent of their participation in the activity. CME for this course is available 09/2011 - 09/2014.

CEUs Credit - The AANEM has designated this live activity for a maximum of 3.25 AANEM CEUs. If purchased, the AANEM designates this enduring material for a maximum of 6.25 CEUs.

2010-2011 Course Committee

Shawn J. Bird, MD, Chair
Philadelphia, PA

Taylor B. Harrison, MD
Atlanta, GA

A. Arturo Leis, MD
Jackson, MS

Gary L. Branch, DO
Owosso, MI

Laurence J. Kinsella, MD
Saint Louis, MO

Marcy C. Schlinger, DO
Okemos, MI

Lawrence W. Frank, MD
Elmhurst, IL

Shashi B. Kumar, MD
Tacoma, WA

Benjamin S. Warfel, MD
Lancaster, PA

2010-2011 AANEM President

Timothy R. Dillingham, MD, MS

Milwaukee, Wisconsin
Crossfires: Piriformis Syndrome, Thoracic Outlet Syndrome, and Tarsal Tunnel Syndrome

Faculty

**Shawn J. Bird, MD**
Professor of Neurology
Director, Electromyography and Neurodiagnostic Laboratories
Department of Neurology
University of Pennsylvania
Philadelphia, Pennsylvania

Dr. Bird is director of the Electromyography Laboratory and Clinical Neurophysiology Fellowship Program, as well as the Myasthenia Gravis Clinic at the University of Pennsylvania. He is a professor of neurology at Penn. He received undergraduate degrees in electrical engineering and biology from Cornell University. He attended medical school at the Johns Hopkins University School of Medicine. He completed his neurology residency and fellowship training in neuromuscular disease and electrodiagnostic medicine at the University of Pennsylvania. He is a fellow of the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM), is currently chair of the AANEM's Course Committee, and has served on the Journal, Special Interest, and Historical committees. He is a fellow of the American Academy of Neurology and the American Neurological Association. His main research interests include neuromuscular disorders associated with critical illness, immune-mediated neuropathies, and myasthenia gravis.

**Loren M. Fishman, MD**
Assistant Professor
Columbia College of Physicians and Surgeons
Medical Director
Manhattan Physical Medicine and Rehabilitation
New York, New York

After graduate school at Christ Church, Oxford, Dr. Fishman went to medical school at Rush Presbyterian St. Luke’s in Chicago. In a Tufts-Harvard Residency program, and as chief resident at the Albert Einstein College of Medicine, his interest in functional and kinesiological aspects of pathology developed. He has written and edited more than 70 academic articles, chapters, and books on the philosophy of science as well as rehabilitation medicine. His work has been reviewed in articles by Jane Brody of the *New York Times* as well as *Spine, Muscle & Nerve*, and other international periodicals. He is past president of the New York Society of Physical Medicine and Rehabilitation, currently associate editor of Topics in Geriatric Rehabilitation, on staff at Columbia College of Physicians and Surgeons, treasurer of the Manhattan Institute for Cancer Research, and has a private practice in Manhattan.

**Kaj H. Johansen, MD, PhD**
Vascular Surgeon
Swedish Medical Center
Clinical Professor of Surgery
University of Washington School of Medicine
Seattle, Washington

Dr. Johansen is a vascular surgeon in community practice at Swedish Medical Center in Seattle, Washington. A clinical professor of surgery at the University of Washington School of Medicine, he has published over 140 peer-reviewed journal articles and over 50 book chapters. He is a member of the American Surgical Society, was designated a Distinguished Fellow of the Society for Vascular Surgery, and is a past president (1997-98) of the Western Vascular Society. Dr. Johansen has for the past 15 years been deeply involved in the diagnosis and treatment of various forms of thoracic outlet syndrome. He is an original member of the Consortium on Outcomes Research and Education for Thoracic Outlet Syndrome (CORE-TOS) and has contributed three chapters to the new text *Thoracic Outlet Syndrome* (Illig, Freischlag, and Thompson, editors).
Mohammad A. Saeed, MD, MS
Clinical Associate Professor
Department of Rehabilitation Medicine
University of Washington School of Medicine
Electrodiagnosis & Rehabilitation Associates
of Tacoma, P.S.
Tacoma, Washington

Dr. Saeed received his specialty training in physical medicine and rehabilitation at the University of Washington in Seattle. Dr. Saeed is board certified with the American Board of Physical Medicine & Rehabilitation (ABPMR), as well as the American Board of Electrodiagnostic Medicine (ABEM). Following residency, he served in the United States Army at Madigan Army Medical Center in Tacoma, Washington, and from 1981-1982 as chief of the Physical Medicine Service. For the past 26 years, he has been in private practice, now as senior partner with Electrodiagnosis and Rehabilitation Associates. He has served on a number of committees for the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM), including Education, Workshop, Training Program, Program, and Professional Practice. He is also presently serving as secretary of the Washington State Society of Physical Medicine and Rehabilitation. In 2005, Dr. Saeed was honored by receiving the first AANEM Outstanding Advocate Award.

Michael D. Weiss, MD
Associate Professor
Department of Neurology
Division of Neuromuscular Diseases
University of Washington Medical Center
Seattle, Washington

Dr. Weiss received his specialty training in neurology at Georgetown University Hospital in Washington, DC, and in neuromuscular disease at the University of Maryland in Baltimore. He is board certified with the American Board of Psychiatry and Neurology (ABPN) as well as the American Board of Electrodiagnostic Medicine (ABEM). Following fellowship, he served briefly at the Veteran’s Administration Medical Center in Washington, DC, as the assistant director of the EMG Laboratory. For the past 10 years, Dr. Weiss has been director of the EMG Laboratory, director of the Muscular Dystrophy Association/Amyotrophic Lateral Sclerosis Clinic, and founding director of the Neuromuscular Division in the Department of Neurology at the University of Washington Medical Center. He has served on the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) Marketing, Research, and Examination committees and the joint American Academy of Neurology/AANEM Limb Girdle Muscular Dystrophy Guidelines Committee. He is currently on the editorial board of Muscle & Nerve. He has authored or coauthored over 50 journal articles, reviews, and book chapters primarily focused on neuromuscular diseases. In 2009, Dr. Weiss was honored by being elected to the American Neurological Association.

Robert A. Werner, MD, MS
Professor and Chief
Department of Physical Medicine and Rehabilitation
Ann Arbor Veteran’s Administration Medical Center
University of Michigan Health System
Ann Arbor, Michigan

Dr. Werner is a professor in the Department of Physical Medicine and Rehabilitation (PMR) and chief of the PMR service at the Ann Arbor Veteran’s Administration (VA) Medical Center. He also has a faculty appointment in occupational medicine within the School of Public Health and in the Center for Ergonomics within Industrial and Operations Engineering. He is a 1983 graduate of the University of Connecticut’s School of Medicine and completed his PMR residency at the University of Michigan Medical Center. He completed a research fellowship sponsored through the National Institute on Disability and Rehabilitation Research in 1991. Dr. Werner’s interests include electromyography, pain management, and industrial rehabilitation. Dr. Werner is codirector of the Ann Arbor VA Chronic Pain Clinic. He has over 70 publications in peer-reviewed journals and has been successful in receiving grant funding from several sources including the National Institute of Health, the Center for Disease Control, the National Institute for Occupational Safety and Health, Johns Hopkins University Center for Visual Display Terminals and Health Research, and the United States Postal Service. Dr. Werner has received awards for research writing from the Association of Academic Physiatrists, the American Academy of Physical Medicine and Rehabilitation, and the American College of Occupational and Environmental Medicine. Dr. Werner is on the editorial board for Archives of Physical Medicine and Rehabilitation, Muscle & Nerve, Journal of Occupational Rehabilitation, and Topics in Stroke Rehabilitation.
Neurogenic Thoracic Outlet Syndrome is Overdiagnosed: Wilbourn Revisted

Shawn J. Bird, MD
Professor of Neurology
Director, Electromyography and Neurodiagnostic Laboratories
Department of Neurology
University of Pennsylvania
Philadelphia, Pennsylvania

INTRODUCTION

Neurogenic thoracic outlet syndrome (TOS) remains one of the more controversial entities in the field of neuromuscular medicine. This topic has been in the center of debate in the literature and this Crossfires course periodically over the past decades. It remains a confusing topic due to the presence of several subtypes, the input from various medical specialties with differing views on this clinical topic, the lack of any agreed-upon diagnostic criteria, and the lack of any randomized, blinded therapeutic clinical trials.

TOS has a long history dating back more than a century. It was considered a common cause of distal hand symptoms for several decades prior to the identification of carpal tunnel syndrome and cervical radiculopathy and before more modern diagnostic approaches (electrophysiology and imaging studies) were applied. TOS has been classified in several ways throughout the years, but most recently the classification is based on the known or presumptive structure being compressed.

There are several subtypes of TOS, which consist of vascular TOS (arterial or venous), true neurogenic TOS, and disputed neurogenic TOS. The vascular and true neurogenic forms are generally agreed upon by most in the medical community. This likely is due to the fact that they share several important features in common, including a consistent clinical presentation, objective confirmatory laboratory diagnostic studies, and a low incidence. The controversy generally is confined to disputed neurogenic TOS, which proponents lump together with the true form of neurogenic TOS.

The anatomy of the thoracic outlet includes the neurovascular supply of the upper extremity. This includes the subclavian artery, which leaves the thoracic outlet after arching over the first thoracic rib, anterior to the scalenus medius and posterior to the scalenus anticus muscle. The brachial plexus follows the same course as the subclavian artery but it is posterior and superior to the artery. The subclavian vein passes anterior to the scalenus anticus muscle. These neurovascular structures are located in the space between the first thoracic rib and clavicle, the costoclavicular space.

The vascular form of TOS, arterial or venous, generally produces vascular symptoms in the limb and does not fall under the purview of neuromuscular clinicians. Briefly, the arterial form of TOS primarily involves compression of the subclavian artery at the base of the neck by a large bony anomaly, usually a cervical rib. Downstream emboli may result from this compression and cause distal limb ischemia. Venous vascular TOS is a rare unilateral disorder that occurs with compression of the subclavian vein near its origin, also in the setting of a cervical rib or bony anomaly. This results in swelling, cyanosis and pain in the upper arm. These entities are confirmed by demonstrating the vascular compression by either invasive or noninvasive vascular studies. The vascular form of TOS can produce distal limb pain, numbness, and weakness, but that is due to the ischemic limb and not compression of the nerves in the thoracic outlet.

TRUE NEUROGENIC THORACIC OUTLET SYNDROME

True neurogenic TOS is a rare disorder with distinct examination and electrophysiologic findings that occur in the setting of a
specific bony anomaly. This anatomic anomaly consists of either a small rudimentary cervical rib or an elongated C7 transverse process, associated with a taut fibrous band that extends from the bony anomaly to the first thoracic rib. It usually is unilateral and occurs more often in young women from the late teens to the 40s. It is clinically manifest by slowly progressive medial hand and forearm numbness with atrophy and weakness in the intrinsic hand muscles. There may be medial arm pain, but this is predominantly a slowly progressive motor disorder. This relatively painless disorder is associated with dramatic neurologic and electrodiagnostic (EDX) findings. As such, there is substantial agreement regarding the existence and manifestations of this disorder.

The classic examination finding in a patient with true neurogenic TOS is the Gilliatt-Sumner hand, where there is dramatic weakness and atrophy in the abductor pollicis brevis (APB) muscle, with lesser involvement of the interossei and hypothenar muscles (Fig. 1). This is believed to be due to the proximal portion of the lower trunk of the brachial plexus, the T1 root in particular before it completely fuses with C8, being stretched over the taut fibrous band. This would more severely affect the T1 component of the lower trunk and produce more atrophy in the APB muscle (Fig. 2). Neurogenic TOS also produces sensory loss in a lower trunk, brachial plexus distribution.

The electrophysiologic findings in true neurogenic TOS include those expected with axonal loss in the lower trunk of the brachial plexus. This includes low, or absent, ulnar and medial antebrachial cutaneous sensory nerve action potentials. As the disorder progresses, there are low amplitude or absent median and ulnar compound motor action potentials. Needle electromyography (EMG) shows denervation with chronic neurogenic motor unit action potential abnormalities in the distribution of the lower trunk of the brachial plexus. The medial antebrachial cutaneous sensory response is a sensitive measure in the diagnosis of neurogenic TOS. The medial antebrachial cutaneous sensory response amplitude appears to fall in parallel with the median motor abnormalities found in the APB muscle. This supports the speculation that the predominant injury in neurogenic TOS is to the T1 component of the lower trunk of the brachial plexus.

When the presence of true neurogenic TOS is confirmed with the classic examination and EDX findings, the treatment consists of surgically sectioning of the congenital band. The sensory and motor deficits typically persist, although any further progression is arrested. The two most commonly used surgical approaches for treatment of TOS are the anterior supraclavicular and the transaxillary approach to resect the band and/or cervical rib. Major neurovascular complications have been reported with both. The anterior supraclavicular approach is favored by most neurosurgeons. Currently, there is no evidence from randomized clinical trials, or other high quality evidence, that would establish the preferred surgical approach for TOS. The appropriate choice of treatment is still based on the preference of the treating physician.

**DISPUTED THORACIC OUTLET SYNDROME**

The greatest proportion of patients who carry the putative diagnosis of TOS have the type referred to as “disputed” TOS by the doubters of this entity and “symptomatic” TOS, or simply neurogenic TOS by its proponents. The many surgical proponents of this disorder did not distinguish between true neurogenic TOS and this disputed form of TOS, lumping them together as if they were part of the spectrum of one single entity. However, this is undoubtedly an error in that these entities are so distinct that they are very unlikely to be part of the same process. The contrast between these two types of TOS is striking, in that the true neurogenic form of TOS is characterized by relatively painless, motor deficits in which the neurologic and EDX findings are dramatic, as opposed to the disputed form of TOS which is predominantly a pain syndrome with no objective neurologic or EDX abnormalities.

Although there is a lack of any objective examination and electrophysiologic abnormalities in disputed TOS, its proponents use subjective complaints with various physical examination maneuvers as support for its existence in individual patients. One of the primary examination criteria for the diagnosis of TOS has been reported to be a positive Adson’s maneuver. However, this diagnostic sign was shown decades ago to be positive in many normal, asymptomatic individuals. The high incidence

---

**Figure 1.** The Gilliatt-Sumner hand in true neurogenic thoracic outlet syndrome. Severe thenar wasting is observed.

With permission from Gilliatt, LeQuesne, Logue, and Sumner.

**Figure 2.** True neurogenic thoracic outlet syndrome. A ligamentous band extends from the C7 transverse process to the first thoracic rib. The proximal part of the lower trunk, particularly the T1 component, is stretched across the taut band.

With permission from Levin, Wilbourn, and Maggiano.
of false-positive results is especially notable when combining various physical examination maneuvers used for the diagnosis of neurogenic TOS. For example, in one study 64 normal individuals were subjected to four examination maneuvers used for the clinical diagnosis of TOS. This included Adson’s test (turning the head to 90 degrees toward the tested arm, while maintaining deep inspiration), the costoclavicular or Halstead test (bracing the shoulders back and down in an exaggerated military posture), an erect hyperabduction test (abducting the arm through 180 degrees while standing), and a supine hyperabduction test. In the majority of normal individuals (58%) complete abolition of the radial pulse was demonstrated in at least one of the clinical tests in one arm.10 Another study looked at the rate of TOS shoulder maneuvers in 53 healthy subjects. These individuals were assessed with Adson’s test, the costoclavicular maneuver, the elevated arm stress test (Roos test), and the supraclavicular pressure test. In this study of these maneuvers and healthy subjects, the outcomes of pulse alteration or paresthesias were unreliable in general.11

The electrophysiology in this subgroup of patients is normal.1,3,4 Some have advocated conduction studies across the brachial plexus and claim that this may provide useful diagnostic information in disputed neurogenic TOS. However, there are marked limitations to this technique that do not allow distinction from normal individuals in a reliable manner. Even the rational for such studies is flawed. If, as proposed by the believers of this methodology, there is nerve compression producing a segment of demyelination proximally in the plexus, then any slowing across that segment would certainly be diluted out by the large segment of nerve undergoing study. There are no studies that substantiate the role of such techniques in the diagnosis of neurogenic TOS. One prominent attempt to show such slowing across the plexus in a patient with neurogenic TOS12 was subsequently shown to be fraudulent with a fabricated photograph.13

The lack of any objective neurologic examination or electrophysiologic abnormalities in the disputed form of TOS is not due to the fact that these patients are at the milder end of a spectrum, with patients with true neurogenic TOS at the other end. As described above, patients with true neurogenic TOS have a stereotypical clinical presentation, neurologic examination, electrophysiologic findings, and an associated anatomic bony abnormality. There is no cohort of patients with disputed neurogenic TOS who have been reported to worsen and develop the weakness, atrophy, sensory loss, and electrophysiologic findings seen in true neurogenic TOS. In this regard, disputed TOS is unlike any other form of compressive neuropathy, such as ulnar neuropathy at the elbow or radiculopathy. In the latter disorders, the early mild manifestations of nerve compression may be purely symptomatic, but many, if not most, patients ultimately develop objective neurologic and electrophysiologic abnormalities. This difference between disputed neurogenic TOS and other well-established forms of compressive neuropathy alone is sufficient in the mind of many peripheral nerve specialists to doubt the very existence of this disorder.

The treatment of disputed TOS is as controversial as the entity itself. Surgical intervention is routinely offered by surgeons to patients who have persistent symptoms after conservative management. However, high-quality evidence for the effectiveness of surgical treatment of disputed neurogenic TOS is lacking. In a study from Colorado,14 it was pointed out that patients who do not have private insurance or worker’s compensation rarely are diagnosed as having TOS and Medicaid patients almost never undergo surgery. The surgery is also not without substantial risks. These include postoperative brachial plexopathy, pneumothorax, and hemorrhage. In some patients the outcome can include severe brachial plexopathy.15

There is evidence that supports the view that surgery is no better than conservative management in this group of patients with neurogenic TOS. One study evaluated a population-based cohort of injured workers in Washington state.16 In this study, Franklin and colleagues compared 158 patients who underwent TOS surgery to 95 patients with TOS who did not have surgery. Sixty percent of workers who underwent surgical treatment were still work-disabled 1 year after surgery. Compared with the workers who had a diagnosis of TOS but did not undergo surgery during a comparable time period, workers who received TOS surgery were three to four times more likely to be work disabled and had 50% greater medical costs. The proportion of workers with acute complications following surgery was approximately 30%.

Nonsurgical treatment appears to have reported beneficial outcomes comparable to surgically-treated patients. For example, one study prospectively evaluated 119 patients with the diagnosis of TOS who had conservative treatment with tailored home exercises.17 The patients were followed for a mean period of 24 months. At the followup examination, 88% of the patients were satisfied with the outcome of the treatment. Seventy-three percent of the patients returned to work during the therapy. However, there have been no head-to-head, randomized clinical trials comparing surgical treatment to conservative treatment in this cohort of patients. A recent systematic review of the available literature regarding the treatment for TOS concluded that there is not currently enough high-quality evidence that any intervention for TOS is helpful.9

The reasons that this form of TOS is controversial and likely substantially overdiagnosed are summarized by the following points (as adopted from Wilbourn8): (1) it has an extraordinarily high incidence, particularly compared to all other established forms of brachial plexopathy; (2) it produces no objective neurologic deficits; (3) the examination “findings” typically consist of various maneuvers with poor specificity; (4) it produces no EDX abnormalities; (5) it is most commonly diagnosed by surgeons who have no experience in the diagnosis of peripheral nerve disorders and have an inherent conflict of interest in surgical treatment; (6) the symptoms reported by many patients often are in the setting where secondary gain is obvious; (7) there is no high-quality evidence that surgical intervention is more effective than nonsurgical management, or even observation; and (8) it most commonly occurs in the setting of personal injury litigation.

REFERENCES

NEUROGENIC THORACIC OUTLET SYNDROME IS OVERDIAGNOSED: WILBOURN REVISTED

Neurogenic Thoracic Outlet Syndrome is Underdiagnosed: The Roos-Wilbourn Debate Revisited

Kaj H. Johansen, MD, PhD
Vascular Surgeon
Swedish Medical Center
Clinical Professor of Surgery
University of Washington School of Medicine
Seattle, Washington

BACKGROUND

The 1998 Annual Meeting of the American Association for Neuromuscular & Electrodiagnostic Medicine (AANEM) was the scene of a Crossfire debate between two icons of contemporary thought regarding the question of neurogenic thoracic outlet syndrome (NTOS). One, David B. Roos, MD, was a widely-published and extremely experienced authority regarding the diagnosis and surgical management of NTOS. The other, the late Asa Wilbourn, MD, was a senior neurologist and electrodiagnostic (EDX) physician at the Cleveland Clinic whose skepticism regarding NTOS had enlivened public discussion and the published literature for the prior 2 decades.

In their presentations Drs. Roos and Wilbourn adopted widely different approaches in support of the postures they were defending. Roos, conceding that some physicians overdiagnose and overtreat patients potentially harboring NTOS (and roundly condemning them), nonetheless strongly supported his posture that NTOS is underdiagnosed. However, he did so predominantly by resorting to appeals to authority (“I have been working with NTOS patients for 30 years, and have had 5,700 patients referred nationally and internationally . . .”) and emotion (“To deny [the existence of NTOS] . . . is to condemn many young, active people in serious trouble to a hopeless life of misery and despair”).

Wilbourn, on the other hand, leveled criticisms at the proponents of the diagnosis of NTOS which included “. . . almost all of these concepts (regarding the possible neuroanatomy of NTOS) lack factual underpinnings; consequently they represent very little more than unfettered speculation . . .” and “. . . concerning the operations performed to treat NTOS, Roos creates a false analogy . . .” Wilbourn argued that those who remained skeptical regarding the existence of “disputed” NTOS (a provocative term he had coined himself) could only be mollified by demonstrable, reproducible EDX evidence for neurologic damage in NTOS, or, alternatively, by the performance of a randomized controlled trial (RCT) clearly demonstrating that surgical decompression is better than conservative care.

Thirteen years on, what has been learned about NTOS? Is the medical community closer to an agreed-upon pathogenesis, an accurate and parsimonious diagnostic algorithm, and an effective, safe, and durable treatment for this condition? This discussion will explore contemporary, clinically-useful evidence supporting Roos’s position that NTOS continues to be notably under- (and mis-) diagnosed and will evaluate Wilbourn’s challenge regarding the existence of NTOS and how it is properly identified.

THE DIAGNOSIS OF NEUROGENIC THORACIC OUTLET SYNDROME

A Signal-to-Noise Problem

Certain disease states are readily diagnosed, sometimes from across the room. For others the diagnosis may be more subtle, but performance of the appropriate objective test defines the condition. For still other conditions, their presence is identified in part by a characteristic clinical presentation but to a great extent by the exclusion of other potential competing diagnoses. At the current time the diagnosis of NTOS fits into the last category.
NEUROGENIC THORACIC OUTLET SYNDROME IS UNDERDIAGNOSED

Table 1. Conditions whose symptoms and signs may overlap with those of neurogenic thoracic outlet syndrome

- **Brain and neuraxis**: multiple sclerosis, syringomyelia
- **Cervical spine**: cervical sprain or strain; cervical spondylosis, arthropathy, arthritis; herniated intervertebral disk; cervical radiculopathy
- **Cervical nerves and brachial plexus**: benign and malignant nerves tumors, brachial plexitis and plexopathy
- **Shoulder**: rotator cuff and impingement syndromes, tendinitis
- **Peripheral nerves**: cubital and carpal tunnel nerve compression syndromes
- **Upper truncal myofascial disorders**: fibromyalgia, polymyalgia rheumatica, myositis
- **Miscellaneous**: temporomandibular joint disorders, migraine, apical pulmonary or pleural tumors, direct brachial plexus trauma

A myriad of patients have neck pain which is associated with various symptoms in the upper extremity. A wide range of pathologic states may be operative in these situations, starting within the brain or the neuraxis and extending through the spinal nerve roots, the intervertebral discs, ligaments and neural foramina of the cervical spine, the brachial plexus itself, the shoulder joint and its surrounding structures, the peripheral nerves in the upper extremity, and the skeletal muscles throughout the neck, the upper back, or the forequarter (Table 1). Accurately selecting out those patients whose symptoms arise due to NTOS from among this much larger group of patients with head, neck and upper extremity complaints is difficult. Fortunately, clinical experience and an expert consensus conference have helped to refine the diagnosis of NTOS from this much larger group of patients with upper truncal and extremity symptoms (Table 2).

A cardinal feature of patients with NTOS is that their upper extremity symptoms predictably and reproducibly worsen with the arm abducted in an out front, out to the side, or overhead position. Whether this occurs during provocative tests (Adson’s test, elevated arm stress test [EAST], military brace test, or Wright test) carried out by a physician or as a consequence of various activities of daily living, such provocative worsening of symptoms with arm abduction is a critical feature of the diagnosis of NTOS. Any patient who can drive for more than a few minutes with their hands remaining in the 10 o’clock/2 o’clock position on the steering wheel, who can sweep or vacuum without symptom exacerbation, or who can readily change ceiling light bulbs or blow dry their hair with the affected upper extremity does not have NTOS.

Virtually all patients who turn out to have NTOS have suffered some prior injury. Two broad categories of injury are relevant. Such patients either have suffered some specific trauma (e.g., a cervical hyperextension injury in a rear-end motor vehicle crash, a fall on an outstretched arm, or an object falling on the patient’s head or shoulder) or alternatively occupy some profession or occupation in which the affected extremity is under chronic out front or overhead stress (e.g., dry wall hangers, cosmetologists or beauticians, dental hygienists, grocery checkers, shelf stockers, clerical workers with prolonged keyboarding duties, among others).

The vast majority of soft tissue injuries in general are most symptomatic and most incapacitating at their onset, steadily improving (or at least stabilizing) over time. This is true even for direct brachial plexus injuries (resulting in “true” NTOS), as pointed out by Wilbourn in his presentation at the 1998 AANEM Annual Meeting. In contrast, all those involved with the management of NTOS agree that its symptoms slowly but inexorably worsen, notwithstanding the passage of time, rest, and appropriate physical therapy. This natural history is so consistent among patients ultimately demonstrated to have NTOS that in his own practice this author is skeptical of an NTOS diagnosis in a patient who describes any sort of waxing and waning upper extremity symptomatology.

**Supportive Adjunctive Testing**

Innumerable provocative, imaging, EDX, and other testing modalities have been pursued in efforts to clarify and refine the diagnosis of NTOS. This profusion of diagnostic tests is not unexpected for a condition in which the pathogenesis, the natural history and the effective and durable management remain unclear and, frankly, controversial.

As noted previously, various provocative tests (Adson’s, military brace, or Wright) generally are considered to be unhelpful in the diagnosis of NTOS, primarily because a large proportion of normal asymptomatic subjects will also have a positive response to these tests (i.e., their specificity is low). However, an inability to hold the affected arm(s) in the EAST position for 1 min is strongly supportive of the diagnosis of NTOS. The elevated arm (brachial plexus) tension test—essentially an upper extremity version of the straight-leg raising and Lasègue tests for sciatica—focuses the clinician’s attention on compression and irritation of the brachial plexus at the base of the neck and has been highly correlated with the diagnosis of NTOS in an observational study. Imaging studies of various sorts have been extensively pursued, but aside from the demonstration on chest x-ray of a cervical rib, an abnormal first rib, or an apical pulmonary or pleural tumor, none have been consistently useful in ruling in or out the diagnosis of NTOS. Vascular laboratory testing (subclavian artery and vein duplex scanning or upper extremity digital plethysmography, in each case with the arms in provocative postures) probably is quite sensitive but, like Adson’s test, has a low specificity. In the author’s practice the vascular laboratory evaluation is used to rule in or out the presence of a “tight” thoracic outlet.

Standard electrophysiologic assessment of patients potentially harboring NTOS is almost always either normal or at best nondiagnostic. The reasons for this are anatomic and technical, associated with the difficulty of assessing episodic, only mild-to-moderate brachial plexus compression which occurs at a site too central (and too deep) to permit standard nerve conduction velocity assessment and which results in too little large-nerve fiber damage to cause significant axonal damage or demyelination more peripherally. In other words, standard EDX testing in patients with NTOS is not adequately sensitive to make the diagnosis, and it is
CROSSFIRES: PIRIFORMIS SYNDROME, THORACIC OUTLET SYNDROME, AND TARSAL TUNNEL SYNDROME

Table 2. Diagnosis of neurogenic thoracic outlet syndrome: results of an expert-panel Delphi survey

<table>
<thead>
<tr>
<th>Supportive of the diagnosis of neurogenic thoracic outlet syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Local tenderness over scalene triangle</td>
</tr>
<tr>
<td>• Hand/digit paresthesias with scalene palpation</td>
</tr>
<tr>
<td>• Known presence of a cervical rib</td>
</tr>
<tr>
<td>• Symptom exacerbation with overhead arm use</td>
</tr>
<tr>
<td>• Thenar or hypothenar atrophy</td>
</tr>
<tr>
<td>• Positive supraclavicular Tinel’s sign</td>
</tr>
<tr>
<td>• Weakness of handgrip, intrinsic hand muscles, or digit or digit V</td>
</tr>
<tr>
<td>• Diminished sensation in digits IV and V</td>
</tr>
<tr>
<td>• Paresthesias in digits IV and V</td>
</tr>
<tr>
<td>• Repetitive strain activities</td>
</tr>
<tr>
<td>• Paresthesias radiating from the supraclavicular space</td>
</tr>
<tr>
<td>• Positive 1-minute EAST</td>
</tr>
<tr>
<td>• Ulnar nerve distribution paresthesias</td>
</tr>
<tr>
<td>• Symptoms exacerbated by driving</td>
</tr>
<tr>
<td>• Paresthesias radiating through arm to hand</td>
</tr>
<tr>
<td>• Hand or digit paresthesias with pectoralis minor tendon palpation</td>
</tr>
<tr>
<td>• Hand or digit paresthesias on passive arm elevation</td>
</tr>
<tr>
<td>• Hand weakness, clumsiness, and “drop attacks”</td>
</tr>
<tr>
<td>• Palpable scalene muscle spasm</td>
</tr>
<tr>
<td>• Prior ipsilateral clavicular or first rib fracture</td>
</tr>
<tr>
<td>• Arm or hand weakness</td>
</tr>
<tr>
<td>• Symptoms begin after injury at work/change in work activity</td>
</tr>
<tr>
<td>• Positive upper limb (brachial plexus) tension test</td>
</tr>
<tr>
<td>• Symptoms exacerbated by work-related activities</td>
</tr>
<tr>
<td>• Occupation or recreation resulting in overhead activities</td>
</tr>
<tr>
<td>• Hand or digit numbness</td>
</tr>
<tr>
<td>• Tenderness to palpation over pectoralis minor tendon/muscle</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rules out the diagnosis of neurogenic thoracic outlet syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Negative 3-minute EAST</td>
</tr>
</tbody>
</table>

*Among the 118 initial items assessed under “Clinical Diagnosis” these 28 had a mean score >3.0 on a 0-5 scale among 12 expert panelists. Cronbach’s alpha (a measure of internal test consistency: values >0.90 suggest excellent group consensus) was 0.901.

used predominantly to document the presence of more peripheral nerve compression syndromes arising at the cubital or carpal tunnel. The recent report of consistently-abnormal conduction delays in the median antebrachial cutaneous sensory nerve of patients later demonstrated to have NTOS has been provocative but such testing is not commonly performed, is operator-dependent, and requires validation.

A Semi-Objective “Gold Standard”

Temporary scalene muscle inactivation by percutaneous administration of local anesthetic or botulinum toxin A (Botox) has been reported intermittently for more than 30 years. However, only after several reports of the University of California Los Angeles group, starting in 1998, has the technique of scalene block become widely utilized in support of the diagnosis of NTOS. The general approach has been to administer bupivacaine under needle electromyography (EMG) and/or ultrasound guidance into the anterior scalene muscle, assessing the patient’s response in various categories of pain, numbness, and tingling and range of upper extremity motion on visual analog scales completed by the patient prior and subsequent to the block. In patients with NTOS the beneficial effects of a bupivacaine intrascalenal block generally last for 1-4 hours; among NTOS patients who respond to intrascalenal Botox, relief of symptoms lasts a mean of 3 months.

The value of the scalene block test in the assessment of patients potentially harboring NTOS can hardly be overstated. In patients ultimately demonstrated to have NTOS, a scalene block appears to have a sensitivity well in excess of 90%. The specificity is also likely extremely high. There is no obvious anatomic or pathogenetic basis on which it can be imagined that a scalene block would be positive in the absence of scalene muscle pathology. Because it is now generally agreed that NTOS arises from chronic posttraumatic spasm, hypertrophy, and fibrosis of the anterior and middle scalene muscles, the fact that NTOS symptoms are relieved with temporary inactivation of the offending scalene muscles would appear to make good biologic sense. While the general consensus among workers in the NTOS field is that the patient’s favorable response to a scalene block provides supportive evidence for or against the diagnosis of NTOS, the author generally mandates a positive scalene block in considering further treatment for symptoms otherwise clinically identified as NTOS.

Post Hoc, Ergo Propter Hoc (or, Wilbourn Revisited)

In the 1999 Issues and Opinions commentary arising out of his AANEM Annual Meeting presentation, Wilbourn stated that “...an alternative method for legitimizing disputed NTOS would be for one or more of its surgical treatments to be proven unequivocally beneficial.” He went on to point out that the most credible means of accomplishing this would be by the performance of a randomized controlled trial (RCT) of surgical versus conservative care for NTOS. Wilbourn and Porter published an outline of such a trial in 1992. The authors were specifically intent on assuring that the evaluation of patient outcomes would be “by independent physicians rather than the operating surgeons.”
To date no RCT of surgical versus nonsurgical care for NTOS has been accomplished. In the hierarchy of credible medical evidence, NTOS (like numerous clinical entities) remains incompletely characterized and its management and outcomes incompletely secured. However, in partial response to Wilbourn’s challenge, numerous published series of NTOS surgical treatment outcomes demonstrate success rates which are consistently in the 70-95% range. No reports in the literature of the last decade demonstrate poor outcomes with surgical therapy for NTOS. Notwithstanding the fact that in most of these series the results are being reported by the surgeons who carried out these operations, as well as the fact that surgical techniques vary somewhat and followup is incomplete and relatively short, it is difficult to avoid the conclusion that clinicians confronted with this characteristic clinical syndrome of NTOS are able to identify it accurately and to treat it effectively in a majority of such cases.

SUMMARY AND CONCLUSIONS

The evolution of a hierarchy of medical evidence is one of the major advances of the past 30 years. It has provided a much more rigorous underpinning for the use of medical data in diagnosing, prognosticating, and treating both patients and populations.

But, it is crucial to keep in mind the limitations of medical evidence and to be aware of the obvious fact that physicians cannot be paralyzed in their patient care by the lack of an objective test or a properly-performed meta-analysis. Appendicitis continues to be treated on the basis of clinical judgment, and, despite the introduction of innumerable imaging techniques, the surgeon still finds a normal appendix 10% of the time. So too with NTOS. Even absent a RCT rigorously validating currently accepted surgical therapy, or EDX findings consistently supporting the clinical diagnosis, a large majority of patients identified as having NTOS and treated for it seem to be made better.

The author concedes that Level I evidence is currently lacking to support the diagnosis and treatment of NTOS. But, it seems incumbent upon those reluctant to accept the concept of NTOS as presented here to offer an alternative explication for a stereotypic clinical syndrome which includes:

- upper extremity pain; weakness, numbness, and tingling; symptom worsening with the extremity held out front or overhead.
- steady worsening over time notwithstanding appropriate conservative therapy.
- resolution of all or most symptoms by local anesthetic or Botox denervation of the scalene muscles or, in 70-95% of cases, by surgical dismantling of the scalene muscles.

Clinicians’ failure to recognize this stereotypic series of symptoms and signs is the primary reason neurogenic thoracic outlet syndrome remains underdiagnosed.

REFERENCES

INTRODUCTION

Tarsal tunnel syndrome (TTS) is an entrapment neuropathy of the tibial nerve or its terminal branches at the ankle within the fibro-osseous tunnel as it travels deep to the flexor retinaculum. Keck and Lam first described TTS independently in 1962. Although there have been extensive publications on this topic, controversies still exist, despite there having been many advances in the understanding of the anatomy, pathophysiology, diagnosis, and treatment of TTS and other distal tibial neuropathies. TTS is the most common entrapment neuropathy of the tibial nerve, but it is relatively uncommon. Although the exact incidence is not known, it does depend on the quality and extent of testing conducted by the examiner. It also depends how one defines TTS. However, no population-based studies exist to determine the incidence or prevalence of TTS. In prior publications and in a retrospective review of all cases referred to the authors’ electrodiagnostic (EDX) laboratory over a 2-year period, it was determined that the incidence of TTS or a variant to be 2% of all lower extremity studies and 0.58% of all studies performed (based upon 8,727 consecutive cases). This is in close agreement with the incidence rate of 0.5% reported by Dr. Oh.  

ANATOMY

The tarsal tunnel extends from the distal tibia to the plantar aspect of the navicular and may be divided at the talus into the upper (tibiotalar) tunnel and lower (talocalcaneal) tunnel. The roof of the tarsal tunnel is formed by the flexor retinaculum (laciniate ligament). The floor consists of the medial surface of the talus, the sustentacum tali, and the medial wall of the calcaneus. The superior border is formed by the superficial and deep aponeurotic fascia of the leg and the inferior border by the abductor hallucis muscle. Individual fibrous septae extend from the inner surface of the flexor retinaculum to the periosteum of the calcaneus. Within these septae, besides the tibial nerve, run the posterior tibial artery and vein and the tendons of the tibialis posterior, flexor digitorum longus, and flexor hallucis muscles. The tibial nerve branches into the medial plantar nerve (MPN), lateral plantar nerve (LPN), and the medial calcaneal nerve (MCN), usually within the confines of the tarsal tunnel proper. Baxter’s nerve (also called the “inferior calcaneal nerve,” the “first branch of the LPN,” and the “nerve to the abductor digiti quinti”) commonly branches from the LPN, although it may come off the tibial nerve as a separate branch in up to 46% of feet. In over 90% of the population, the branching of the tibial nerve into the MPN and LPN occurs within the tarsal tunnel region (Fig. 1A).

The LPN also is a mixed nerve. Its sensory fibers provide cutaneous innervation to the lateral aspect of the sole, and to the plantar aspect of the fifth and lateral half of the fourth toes. Its motor innervation includes the quadratus plantae, flexor digiti minimi brevis, flexor hallucis brevis (lateral head), adductor hallucis, all interossei, and second, third, and fourth lumbricals.

Baxter’s nerve innervates the abductor digiti minimi pedis...
(ADMP). It may sometimes send motor branches to the quadratus plantae and flexor digitorum brevis as well. It provides no cutaneous innervation in the foot.

The MCN is a purely sensory branch and provides cutaneous innervation to the posterior, medial, and plantar surfaces of the heel. The MCN has a highly variable course. It usually originates from the tibial nerve but may also arise from the LPN or from the MPN/LPN bifurcation. When originating in the tarsal tunnel, the MCN must pierce the flexor retinaculum on its way to the medial and plantar surfaces of the calcaneal region.

In the lower tarsal tunnel at the level of the calcaneus, the tunnel for the tibial nerve is divided by the interfascicular septum into the upper and lower calcaneal chambers. The deep fascia of the abductor hallucis forms the interfascicular septum when this fascia extends towards its attachments to the medial aspect of the calcaneus. The MPN travels within the upper chamber and the LPN travels within the lower chamber. The MPN or LPN can be entrapped through the calcaneal chambers by the proximal or distal edge of the interfascicular septum.\(^6\)

The tarsal tunnel can be divided into the proximal tarsal tunnel and the distal tarsal tunnel (or porta pedis).\(^11\) Proximal TTS consists of entrapment of the tibial nerve at the retromalleolar region (or at the proximal end of the tunnel with corresponding clinical symptoms). Distal TTS involves one or more terminal branches of the tibial nerve, such as the MPN, LPN, MCN, or Baxter’s nerve. An EDX approach to TTS must consider the fact that pathology can occur in either area. Localized pathology may involve only one of these nerves or branches (Figs. 1A-B).

**ETIOLOGY OF TARSAL TUNNEL SYNDROME**

A number of causes have been reported in the literature for TTS, and these have been classified into five broad categories: (1) traumatic, (2) compressive (by space-occupying lesions), (3) systemic, (4) biomechanical, and (5) idiopathic.\(^6\)

The most common cause of TTS is trauma, which accounts for the majority of these cases. Cumulative trauma (microtrauma) can be a factor in some cases. Trauma may include fractures of the ankle and foot, ankle sprains, and surgical procedures around the foot and ankle. Some of the other etiological factors are space-occupying lesions, such as ganglia, anomalous or hypertrophied muscles, neurilemoma, schwannoma, tenosynovitis, and chronic thrombophlebitis. Systemic causes include hyperlipidemia, gout, hypothyroidism, acromegaly, rheumatoid arthritis, varicosities, and diabetes mellitus. Biomechanical causes include tarsal joint impaction due to hypermobility of the first ray, rigid joint structures, tarsal joint coalition and rear foot varus.\(^6\) As in carpal tunnel syndrome, the cause of TTS in some cases is unknown.\(^13\)

**CLINICAL FINDINGS**

Typical clinical symptoms include burning pain and paresthesia of the toes and sole of the feet. Classically, the symptoms are worse at night, increased by activity and diminished with rest. There also may be numbness on the plantar aspect of the foot involving one or more of the tibial nerve branches. The most helpful diagnostic criteria are a positive Tinel’s sign at the proximal or distal tarsal tunnel area (sometimes accompanied by tingling discomfort radiating proximally along the course of the nerve, a finding known as the Valleix phenomenon)\(^6\) and objective sensory loss in the territory of any of the terminal branches of the tibial nerve. Provocative testing forcing the heel into maximum inversion or eversion may aggravate the symptoms. Some publications consider the “dorsiflexion–eversion test” as the most sensitive test and very specific.\(^12\) Biomechanical studies have demonstrated that while full eversion decreases tarsal tunnel volume by only 2.5 cm\(^4\) ± 0.9 (\(p<0.001\)), mean pressure increases from 2 mm Hg ± 1 in neutral position up to 32 mm Hg ± 5 with eversion. Pressure in the distal talocalcaneal tunnel is about double that in the proximal tibiotalar tunnel. The distal talocalcaneal tunnel likely is the site of compressive neuropathy when there is an accentuated eversion deformity and pes planus.\(^3\)

It should be noted, however, that not all four branches are affected.
in all cases. Weakness of toe flexion and atrophy of the intrinsic foot muscles are rare and detecting weakness of toe flexion and intrinsic foot muscles can be difficult. Calcaneal branches are often spared, and thus, the heel pad usually has normal sensation. Bilateral TTS is relatively rare and, for bilateral neuritic symptoms, it is important to rule out generalized peripheral neuropathy.

**ELECTRODIAGNOSTIC EVALUATION**

EDX studies should be performed on all patients suspected of having TTS. Motor, sensory, and mixed nerve conduction studies (NCSs) as well as needle electromyography (EMG) can help confirm the diagnosis of TTS in over 90% of cases. Motor NCSs of the tibial nerve are not as helpful because of their low sensitivity. Prolonged terminal latency of the tibial nerve was observed in 47% of the cases.

Galardi and colleagues reported in a case series that only 3 of 13 patients had abnormal motor studies and that these patients also always had abnormalities of mixed and sensory nerves. Absence of the sensory nerve action potential (SNAP) was the most frequent abnormality. SNAPs were also absent from the two unaffected limbs. Mixed NCSs were abnormal in 85.7% of TTS limbs, but normal in all asymptomatic limbs and control subjects. Mixed NCS abnormalities were always associated with abnormal sensory NCSs.

In one series, near-nerve sensory NCSs of the MPN and LPN were abnormal in more than 90% of the cases. The MPN, LPN, and Baxter’s nerve always should be tested, because only one may be affected in some cases.

Felsenthal and colleagues described a technique of motor NCSs of the tibial nerve across the tarsal tunnel. It established both a distal latency across the abductor tunnel as well as proximal latency across the tarsal tunnel. Abnormalities could be diagnosed using the decrement of the amplitude across the tarsal tunnel or abnormal latency across the tarsal tunnel. It should be noted that the muscle described for pickup from the lateral plantar nerve as the ADMP is undoubtedly primarily from the muscle belly of the flexor digiti minimi brevis in light of research published by Del Toro and colleagues.

It is generally agreed that the most sensitive test for possible compromise of the MPN, LPN, or tibial nerve is some form of sensory NCSs. There are two methods for performing pure sensory NCSs of the plantar nerves: one using the surface recording electrodes and the other sensory near-nerve needle electrodes. Pure sensory potentials can be recorded from the tibial nerve proximal to the flexor retinaculum (orthodromic technique) or by stimulating the tibial nerve and recording form the first and fifth digits (antidromic technique). Responses recorded with these techniques are generally small, even with extensive signal averaging. SNAP studies have two main disadvantages: (1) they are time consuming and unpleasant for some patients and (2) there may be no SNAPs in some normal subjects. In this author’s experience, even with averaging, pure sensory responses are difficult to obtain in healthy subjects. Galardi and colleagues also found no plantar sensory responses in 8% of the normal subjects. The near-nerve techniques can be quite time consuming and uncomfortable for the patient. However, this is the only viable technique for EDX evaluation of interdigital neuropathy.

Saeed and Gatens described a technique for mixed NCSs of the MPN and LPN. This method records the mixed nerve action potentials from the tibial nerve with a bar electrode placed behind the medial malleolus. They found the mixed NCSs for the MPN and LPN, which predominately test the sensory fibers, to be more practical and clinically useful because they can be performed quickly and easily. However, in patients with thick calluses it can be difficult to stimulate the MPN and LPN on the plantar surface of the foot. Ankle edema or swelling may cause difficulty with recording the response and may require recording needle electrodes. In older patients (especially those over the age of 70), if the responses are absent on both sides, interpretation should be made with caution. Despite these technical difficulties, mixed NCSs of the MPN and LPN are the most easily performed and reliable techniques available.

Many prefer the Saeed and Gatens’ technique because it is easy and has the advantage of not requiring a signal average. Galardi and colleagues in 2000 reported their findings after comparing motor, orthodromic sensory, and mixed NCSs for the MPN and LPN in patients with TTS. They found the sensory and mixed NCSs to be much more sensitive than the motor NCSs. Although mixed NCSs are less sensitive, they are more specific than sensory NCSs. They recommended mixed NCSs because of the decreased likelihood of false-positive results, especially for presurgical diagnosis of TTS.

Somatosensory evoked potentials rarely are used for the evaluation of TTS. This requires special expertise and should be performed only after more routine studies fail to document an abnormality.

Needle electrode examination of intrinsic foot muscles is important

---

**Table. Differential diagnosis of tarsal tunnel syndrome**

- Proximal or “true” TTS (upper tibiotalar tunnel)
- Distal TTS (lower talocalcaneal tunnel)
- Medial plantar neuropathy in the distal tarsal tunnel or abductor canal
- Lateral plantar neuropathy in the distal tarsal tunnel or abductor canal
- Chronic compressive medial and/or lateral plantar neuropathy
- Medial calcaneal neuropathy
- “Baxter’s neuropathy” (or inferior calcaneal neuropathy)
- Generalized peripheral neuropathy
- Distal tibial neuropathy secondary to, or, TTS complicated by, generalized peripheral neuropathy
- Proximal tibial neuropathy
- Sciatic neuropathy, lumbosacral plexopathy, or radiculopathy
- Musculoligamentous: plantar fasciitis, soft tissue sprains/strains, tenosynovitis, and bursitis

TTS = tarsal tunnel syndrome

---

**CROSSFIRES: PIRIFORMIS SYNDROME, THORACIC OUTLET SYNDROME, AND TARSAL TUNNEL SYNDROME**

[Table]
When a peripheral neuropathy is present, it is difficult to diagnose the presence or absence of MPN and LPN nerve compression but in this case comparison of the peroneal motor compound motor action potential (CMAP) with tibial motor CMAP may be helpful.

The MPN or LPN can be entrapped through the calcaneal chambers by the proximal or distal edge of the interfascicular septum. Symptoms may be in the distribution of the MPN, LPN, or both depending upon which nerve is involved. There may be vague pain on the medial side of the foot. A positive Tinel’s sign may be present at the exit point of the tarsal tunnel or along the length of the interfascicular septum to its distal edge just proximal to the abductor canal.

NCSs may demonstrate both prolonged latencies or small motor, sensory, or mixed nerve responses in the affected nerve with no abnormalities observed in other tibial nerve branches. Needle EMG examination will be abnormal in the intrinsic foot muscles supplied by the affected nerve only. Despite refinements in EDX techniques, it can be difficult to diagnosis true TTS or to distinguish it from other focal or generalized neuropathies.

**MEDIAL PLANTAR NEUROPATHY IN THE ABDUCTOR CANAL**

The MPN can be compressed in isolation along its pathway distal to the tarsal tunnel. The common site of compression is at the abductor tunnel (the fibromuscular tunnel) behind the navicular tuberosity (Fig. 1). Reversible medial plantar neuropathy among joggers (jogger’s foot) has been described. Apparently, prolonged running with a valgus running style produces repeated injury to the MPN at the abductor tunnel. Clinically, these patients have burning or tingling over the medial sole and tenderness over the MPN at its entrance to the abductor tunnel. NCSs and needle EMG examinations demonstrate abnormalities similar to those seen with MPN entrapment by the interfascicular septum.

**LATERAL PLANTAR NEUROPATHY IN THE ABDUCTOR CANAL**

The LPN can be compressed along its pathway distal to the tarsal tunnel, causing a lateral plantar neuropathy. Sensory loss is confined to the lateral sole. NCSs and needle EMG examinations demonstrate abnormalities similar to those seen with LPN entrapment by the interfascicular septum. Terminal latency to the flexor digiti minimi brevis (FDMB) muscles may be prolonged and the CMAP may be small. Mixed or sensory LPN latencies may be prolonged or the response abnormal or absent. Needle EMG may show signs of denervation in the FDMB or dorsal interosseous muscles.

**MEDIAL CALCANEAL NEUROPATHY**

Medial calcaneal neuropathy often presents pain and paresthesias along the medial aspect of the heel without any weakness. The pain tends to worsen with ambulation. It is common to have local tenderness or a Tinel’s sign over the MCN and numbness and tingling over the medial side of the heel. Diagnosis of MCN neuropathy can be confined by NCSs of the MCN. This should include side-to-side comparison of the MCN SNAP amplitude...
and latency. The MCN response usually is small and difficult to obtain in some normal individuals. Its clinical usefulness is still questionable.

**INFERIOR CALCANEAL/BAXTERS’ NEUROPATHY**

The inferior calcaneal nerve (ICN) commonly branches from LPN but it has been found to come off the tibial nerve as a separate branch in up to 46% of feet. ICN neuropathy usually presents as chronic anterior or medial heel pain. The symptoms are precipitated by sports in some cases. This nerve provides motor innervation to the ADQP as well as innervation to the periosteum of the calcaneus. EDX abnormalities may include prolonged latency to the ADQP as well as membrane instability and decreased motor unit recruitment and a small ICN CMAP.

**DIFFERENTIAL DIAGNOSIS**

EDX evaluation is very important in defining the presence or absence of neuropathic disorders (Table). Distal mononeuropathies, such as medial or lateral plantar neuropathies and proximal nerve lesions like sciatic or tibial neuropathy in the popliteal fossa and thigh, can mimic TTS. In cases of sciatic or proximal tibial neuropathy, there will be an abnormal sural NCS and an abnormal needle EMG of the tibial-innervated muscles proximal to the ankle. L5 or S1 radiculopathy can be present with symptoms limited to the sole of the foot, but a needle examination may reveal abnormalities in L5- or S1-innervated muscles proximal to the foot, and—in case of S1 nerve root compromise—the H-reflex study will be abnormal. Ischemic monomelic neuropathy, a disorder characterized by acute onset burning pain in the foot or toes resulting from arterial occlusion usually between the hips and knees, may be confused with TTS. Certain musculoskeletal disorders can simulate TTS. Plantar fasciitis characteristically causes foot pain when standing up in the morning, localized at the origin of the plantar fascia at the calcaneus, whereas TTS tends to produce medial heel and arch pain along the abductor hallucis muscle and sensory symptoms. Plantar fasciitis is associated with localized tenderness, but nocturnal paresthesias are more common with TTS. Foot pain also may be due to orthopedic causes such as collapsed metatarsal heads or longitudinal arch strain and rheumatological disorders such as ankylosing spondylitis and gout. EDX studies typically are normal if the foot symptoms are due to these musculoskeletal causes.

Plain radiography examination of the foot can identify displaced fractures, accessory ossicles, and bony exostoses within the vicinity of the tarsal tunnel. Weight-bearing radiographs may demonstrate foot deformities.

Magnetic resonance imaging (MRI) is effective for assessing the contents of the tarsal tunnel and the branches of the tibial nerve. It is especially useful in post-traumatic cases and space-occupying lesions. In cases of failed tarsal tunnel release, MRI is recommended to assess the neural and surrounding structures. Ultrasonography may be of value in some cases, especially detecting cysts and ganglia.

**TREATMENT**

The treatment of TTS, which depends on the causes, can be classified into nonoperative and operative. If there is no structural abnormality present, then it is appropriate to begin with conservative treatment removing aggravating factors, such as poorly-fitting shoes, or applying correct foot orthosis.

**Nonoperative Treatment**

Nonsteroidal antiinflammatory drugs and corticosteroid injections are the most helpful in the presence of tenosynovitis and inflammatory arthropathies, such as rheumatoid arthritis or ankylosing spondylitis. Care must be taken to avoid direct injection into the tibialis posterior tendon. Other nonoperative treatments include the use of pressure stockings, to decrease swelling and venous stasis, and programs for weight loss for obese patients. In patients who have symptoms reproduced by dorsiflexion, a heel lift may relieve symptoms by decreasing tension on the tibial nerve. Runners with hyperpronated feet may benefit from a slightly toe in foot-strike to shift pressure to the lateral aspect of the foot, thus decreasing stretch on the tibial deformities.

**Operative Treatment**

When the conservative approach fails, surgical exploration of the tibial nerve or its branches in the foot may be necessary. Nerve compression within the tarsal tunnel in the presence of a space-occupying lesion is an indication for surgical decompression. However, in the absence of any space-occupying lesion or focal compression of the tibial nerve, tarsal tunnel release must be carefully considered. However, if surgery is planned, many strongly advocate release of all four medial ankle tunnels while preserving even small sensory and cutaneous branches. The tarsal tunnel is opened to identify any space-occupying lesions and to identify for anatomic variations of the tibial and calcaneal nerves. The abductor hallucis is retracted while preserving the medial branch to the skin. The roof of the medial and lateral tunnel is incised and the septum between the two tunnels is removed. And, finally, the roof of the calcaneal tunnel is incised. While most establish early postoperative immobilization, others advocate early ambulation and weight bearing using a walker to minimize tension across the ankle incision, which permits gliding of the tibial nerve and its branches and minimizes the risk for fibrosis and nerve adhesion within the surgical bed.

**SUMMARY**

TTS exists, although it is uncommon and sometimes overlooked, especially distal TTS. The most common problem is misdiagnosis or a partially correct diagnosis. TTS often presents with vague symptoms and its signs may be difficult to elicit. The history often reveals prior trauma to the involved ankle. Tinel’s sign may be positive and hindfoot deformity may be present. A complete needle EMG/NCS assessment is required. The standard examination should include a bilateral study and testing for MPN and LPN motor and sensory conductions along with the needle EMG study. MRI can help identify space-occupying lesions. Once the diagnosis has been made, nonsurgical treatment may be indicated. Injections have limited success. If the conservative
nonoperative treatment fails, then surgical decompression is the treatment of choice, although it is important for the operative procedure to release all four tunnels while preserving even small sensory branches and promoting early postoperative mobilization to void adhesions to maximize the likelihood of a good outcome. The literature supports up to an 85-90% rate of improvement or resolution of symptoms with surgical release. However the specific cause of TTS must be addressed.

REFERENCES

Tarsal Tunnel Syndrome is Overdiagnosed

Michael D. Weiss, MD
Department of Neurology
Division of Neuromuscular Diseases
University of Washington Medical Center
Seattle, Washington

INTRODUCTION

Tarsal tunnel syndrome (TTS) is a form of nerve entrapment manifested by burning pain and numbness in the sole of the foot and worsening of symptoms with prolonged standing or walking. The disorder is due to entrapment of the tibial nerve and its branches, the medial and lateral plantar and calcaneal nerves, in the posterior tarsal tunnel, just posterior and inferior to the medial malleolus. TTS is often suggested to be the carpal tunnel syndrome of the lower extremities but suffers from a lack of consensus in regard to its diagnosis, including electrodiagnostic (EDX) testing.

Patients with TTS sometimes present with signs common to peripheral nerve entrapment, including sensory deficits over the plantar surface of the foot in the distribution of the medial and lateral plantar and calcaneal nerves and a positive Tinel’s sign at the ankle just behind the medial malleolus, but sometimes the diagnosis is made based on the history alone. Routine EDX testing does not always correlate with the clinical diagnosis of TTS and occasionally is normal in patients who ultimately are given this diagnosis, some of whom end up undergoing surgical decompression. While no epidemiologic studies exist ascertaining the incidence or prevalence of TTS, given the lack of standardized clinical criteria, symptoms that could be representative of another disorder all together, and few prospective studies demonstrating the utility of EDX testing in suspected TTS, it is likely that this condition is overdiagnosed.

DIFFERENTIAL DIAGNOSIS OF TARSAL TUNNEL SYNDROME

A number of conditions are associated with symptoms that are quite similar to those of TTS and need to be excluded (Table). The differential diagnosis for TTS includes a number of non-neuropathic disorders such as Achilles tendonitis, stress fractures, bursitis, arthritis, peripheral vascular disease, metatarsalgia, and, most importantly, plantar fasciitis. Neuropathic disorders that resemble TTS include S1 radiculopathy, lumbar spinal stenosis, interdigital (Morton’s) neuroma, isolated medial or lateral plantar neuropathies within the foot, and distal sensory polyneuropathy. Three of the most common conditions that resemble TTS are discussed in more detail below.

Plantar Fasciitis

Plantar fasciitis remains among the most common mimics of TTS and is the most common cause of plantar heel pain. Plantar fasciitis is distinguished from TTS primarily by the history of severe heel pain, worse upon rising from a resting position, and reproduction of pain upon palpation of the plantar surface of the heel at the medial calcaneal tubercle. Unlike patients with TTS, the majority of patients with plantar fasciitis typically improve spontaneously, usually within 12 months. The disorder is thought to arise as a consequence of abnormal amounts of stretching of the plantar fascia, sometimes related to activities such as long distance running or prolonged standing. Sometimes it can be associated with rheumatologic disorders such as psoriatic arthritis and ankylosing spondylitis.
may be of value in the treatment of severe S1 radiculopathy. Epidural corticosteroid injections also and oral corticosteroids may be of benefit in the treatment of Short-term use of opioids, antispasmodic agents like baclofen, anti-inflammatory agents and acetaminophen. Physical therapy analgesic and anti-inflammatory medications such as nonsteroidal similar to TTS, can recur. The mainstays of treatment are The symptoms of S1 radiculopathy are often self-limited but, and numbness on the sole of the foot. Sensory nerve conduction lateral aspect of the foot, some patients describe primarily pain and shockwave therapy.

S1 Radiculopathy

If low back pain is limited, S1 radiculopathy can sometimes mimic TTS\(^5\) and lead to failed tarsal tunnel decompression. Though sensory changes occur most commonly over the posterior calf and lateral aspect of the foot, some patients describe primarily pain and numbness on the sole of the foot. Sensory nerve conduction is normal but there may be a prolongation or absence of the H reflex on the affected side. Needle electromyography (EMG) may demonstrate denervation of S1 innervated muscles such as the gluteus maximus, long head of the biceps femoris, gastrocnemius and soleus muscles, and the S1 paraspinal muscles. However, a normal EDX study cannot exclude absolutely the diagnosis of S1 radiculopathy, especially when there is no concomitant weakness. Magnetic resonance imaging may be necessary in such patients to confirm the diagnosis.

The symptoms of S1 radiculopathy are often self-limited but, similar to TTS, can recur. The mainstays of treatment are analgesic and anti-inflammatory medications such as nonsteroidal anti-inflammatory agents and acetaminophen. Physical therapy and temporary activity modification can also accelerate recovery. Short-term use of opioids, antispasmodic agents like baclofen, and oral corticosteroids may be of benefit in the treatment of severe S1 radiculopathy. Epidural corticosteroid injections also may be of value in the treatment of S1 radiculopathy when the pain is debilitating, persistent for weeks or months, and refractory to other therapies.

Distal Sensory Polyneuropathy

For the EDX physician, the primary alternative consideration in the evaluation of TTS is the exclusion of distal sensory polyneuropathy (DSP), especially when the symptoms are bilateral. DSP is not uncommonly misdiagnosed as TTS,\(^6\) especially if EDX testing is obtained only after the patient fails TTS surgery. Sometimes a careful neurologic examination can distinguish between the two conditions in demonstrating sensory loss not only over the sole of the foot but also the dorsum of the foot and toes or reduced deep tendon reflexes at the ankles, neither of which should be seen in TTS. Relying solely on EDX testing to distinguish these disorders can be problematic as the nerve conduction study (NCS) can be normal in pure small fiber polyneuropathies and does not exclude this diagnosis.

An ever increasing number of studies have demonstrated that small fiber polyneuropathies should be considered in patients with unexplained neuropathic foot pain, including burning feet, and that the diagnosis often must be substantiated by specialized testing such as quantitative sudomotor axon reflex testing, quantitative sensory testing, and skin biopsy to determine intraepidermal nerve fiber densities.\(^5,8\) Recent studies suggest that in the setting of small fiber polyneuropathy, skin biopsy has a sensitivity varying from 36 to 88%.\(^7\) Given that many non-neurologists fail to consider small fiber polyneuropathy as an alternative diagnosis to TTS, it is not surprising that TTS is sometimes misdiagnosed with normal EDX evaluation when the appropriate diagnosis is small fiber polyneuropathy.

Treatment for DSP in part depends on the cause. For instance, in patients with diabetic neuropathy, aggressive correction of hyperglycemia can prevent worsening. In patients with impaired glucose tolerance, achievement of euglycemia actually may promote regeneration of sensory nerve axons with concomitant clinical improvement.\(^12\) Unfortunately, many patients with DSP have no recognizable cause. For these patients, treatment is symptomatic and includes a number of neuropathic pain medications. Chief among these include the anticonvulsants gabapentin and pregabalin, tricyclic antidepressants such as amitriptyline and nortriptyline, newer antidepressants including duloxetine, and systemic anesthetics such as mexiletine, tramadol, and opioid medication.

**ELECTRODIAGNOSTIC EVALUATION OF TARSAL TUNNEL SYNDROME**

EDX confirmation of TTS typically involves a combination of sensory and motor NCSs and needle EMG findings with varying degrees of sensitivity. In a study by Galardi and colleagues of 14 patients and 12 control subjects, medial and lateral sensory NCSs demonstrated the greatest yield for detecting TTS, with sensitivities of 93% and 100%, respectively.\(^2\) Prolongation of the tibial distal motor latency had a low sensitivity of 23%.\(^3\) However, while there are numerous publications on the subject, there are few prospective studies to validate the EDX confirmation of TTS, in part because there remain no consensus criteria for a standard case definition of TTS.
From a total of 317 articles published between January 1965 and April 2002 found on Medline, a recent American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) practice group was able to identify only four that met Class III levels of evidence,\textsuperscript{25,10} in particular one prospective study in which the diagnosis of TTS was made by defined clinical criteria independent of the EDX examination and EDX abnormalities that were clearly presented.\textsuperscript{11} To confirm a diagnosis of suspected TTS, the group recommended the following based on their Class III levels of evidence:

- tibial motor NCSs, with responses recorded over the abductor hallucis and abductor digiti minimi pedis muscles, demonstrating prolonged distal onset latency;
- medial and lateral plantar mixed NCSs, demonstrating prolonged peak latency or slowed conduction velocity (CV) across the tarsal tunnel; and
- medial and lateral plantar sensory NCSs, demonstrating slowed CV across the tarsal tunnel and/or small amplitude or absent responses.

There was insufficient evidence to recommend any needle EMG criteria. The group noted that none of these studies were blinded and that the clinical criteria used in the studies was inconsistent and called for the development of consensus criteria for the clinical diagnosis of TTS as well as studies addressing the impact of EDX testing for TTS on therapy and outcomes.

NCSs testing for TTS sometimes are challenging due to a number of technical considerations. Sensory NCSs of the medial and lateral plantar nerves usually cannot be performed recording with surface electrodes and often require near nerve recordings, rendering these techniques challenging to perform. Skin temperature is frequently difficult to maintain above 30°C to prevent artificial prolongation of the tibial distal motor latency or medial and lateral plantar sensory or mixed nerve CV slowing that might mimic TTS. Sensory NCSs in the feet in particular often are difficult for a variety of other reasons as well, including obscuration of the waveforms due to stimulus artifact, calloused feet that may preclude stimulating or recording from the nerve altogether, and small amplitude responses that often need to be averaged a number of times to ensure reproducibility. Additionally, an absent medial or lateral plantar sensory or mixed nerve response may not be interpretable as it frequently is not present in normal individuals over the age of 60 and sometimes even in those younger.

The use of needle EMG to diagnosis of TTS is even more problematic. Needle EMG of the tibial-innervated foot muscles, such as the abductor digiti quinti pedis or abductor hallucis muscles, is challenging given that it is often hard to localize these small muscles and painful for the patient to undergo the study. Also, spontaneous activity in these muscles sometimes can be seen in normal individuals, possibly as a consequence of local foot trauma, as well as in those with other disorders such as distal predominant polyneuropathies and radiculopathies, and, therefore, cannot be used as stand-alone criteria for the diagnosis of TTS.

TREATMENT OUTCOME OF TARSAL TUNNEL SYNDROME

TTS treatment usually is influenced by its cause. If no structural abnormality is found, conservative treatment typically is provided. Conservative treatment includes arch support, orthotics, corticosteroid injections, and neuropathic pain medication including gabapentin. Nerve compression by a space occupying mass within the tarsal tunnel or a failure to respond to more conservative therapy traditionally has been thought to warrant surgical exploration of the tibial nerve or its branches in the foot. However, only a few studies have addressed the outcome of such surgery and none have been blinded or prospective. In one retrospective study, 47 patients over a 10-year period underwent surgical decompression of the tibial nerve at the ankle after an average 16 months of conservative therapy.\textsuperscript{1} Confirmatory NCS abnormalities with suggestive clinical findings (including a Tinel’s sign at the ankle) were found in 81% and 72% demonstrated improvement but the perioperative complication rate was significant at 30%. In a similar study, 60 patients with both a positive Tinel’s sign and tibial motor NCS findings consistent with TTS who underwent tarsal tunnel release demonstrated 85% improvement on objective measures as well as quality of work, job productivity, and interpersonal relationships.\textsuperscript{2} However, other surgical studies have noted more mixed results and not all have required that patients demonstrate electrophysiological abnormalities prior to surgery.\textsuperscript{15}

CONCLUSIONS

Fifty years after Keck and Lam first described TTS,\textsuperscript{6,7} the lack of clear consensus on the clinical diagnosis of this entrapment syndrome and limited validation of EDX testing for this condition remains problematic. As a consequence, there likely are far fewer cases of TTS than suspected, especially those that are neither post-traumatic nor associated with a space occupying lesion. There are many conditions that resemble TTS that need to be considered prior to making this diagnosis. A careful clinical examination needs to be performed on any patient with symptoms suggestive of TTS. Alternative diagnoses such as DSP or S1 radiculopathy need to be ruled out if the clinical findings are inconsistent with TTS, such as sensory loss on the dorsum of the foot or on the leg or decreased ankle reflexes. In keeping with the 2005 AANEM guidelines, EDX testing should demonstrate a combination of medial and lateral plantar sensory or mixed nerve abnormalities and/or prolonged tibial distal motor latencies. Additionally, there should be preservation of sural and superficial peroneal sensory nerve conduction. Needle EMG changes in the foot should never be used as definitive evidence for TTS when seen in the absence of NCS abnormalities. Surgery for TTS should be reserved for refractory patients with severe pain and definitive clinical and EDX findings.
TARSAL TUNNEL SYNDROME IS OVERDIAGNOSED

REFERENCES

Although piriformis syndrome (PS) has remained a somewhat elusive diagnosis at best, and a diagnosis of exclusion at worst, new developments have altered the clinical approach to it and to a small number of related neuromuscular diatheses. This discussion is intended to adumbrate and describe the new information and techniques, analyze their individual validity and possible joint utility for clinicians.

PART ONE: STEWART CRITERIA AND REPLY

At the Crossfires debate in Monterrey, California, at the 2005 American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) Annual Meeting, both Professor Ernie Johnson and Dr. Robert Werner maintained that PS was a spurious entity and that the electrophysiological tests for it were inconclusive, misleading, and possibly not very smart. Dr. Johnson commented that PS was not even mentioned in *Fundamentals of Neurology* by Sutherland. But of course neither was chronic inflammatory demyelinating polyneuropathy, acquired immune deficiency syndrome, or the genetic code, for that matter.

At the 2010 American Academy of Physical Medicine and Rehabilitation (AAPM&R) Annual Meeting it was suggested that brief, acute compression or stretching of the sort under discussion here does not alter nerve conduction velocity (NCV). But even a cursory review of the literature suggests otherwise, some excluding ischemia and histological damage to nonsteroids on the NCV changes in acute compression, and at least one study to the contrary.

On logical grounds, any diagnosis of exclusion is bound to be underdiagnosed. If something is a diagnosis of exclusion, there must be other diagnoses that fit the same symptom set. Therefore, it will be possible that a patient will have both the diagnosis of exclusion and some other diagnosis. But, in those cases, by definition, the diagnosis of exclusion is not considered (Fig. 1).

Comparing the posterior tibial and peroneal H reflexes elicited in the anatomical position with these same reflexes studied in

---

The woman with almost everything

*Figure 1.* This Boolean depiction of some of the possible options illustrates how, if poison ivy were a “diagnosis of exclusion,” no case of poison ivy in patients (also having similar dermatological conditions) would ever be diagnosed.
the flexion, adduction, and internal rotation (FAIR) test was then described as a way of lifting PS out of the dusky chambers of “diagnosis of exclusion,” and into the electrodiagnostic light of day: does the FAIR position significantly prolong the H-reflex latency (a binary decision procedure) (Fig. 2).

The substance of that debate, as well as a fair amount more, was put into print in 2003 when Muscle & Nerve published a debate between Dr. John Stewart, a neurosurgeon at McGill University, on the one hand, and Dr. Michael Shaffer, of the Mayo Clinic, and me, on the other, regarding whether PS is over or underdiagnosed.9,10

In his contribution, entitled “The piriformis syndrome is overdiagnosed,” Dr. Stewart, proposed five criteria “ideally” to define PS:

1. Presence of symptoms and signs of sciatic nerve damage.
2. Presence of electrophysiological evidence of sciatic nerve damage.
3. Imaging of the lumbosacral nerve roots and of the paravertebral and pelvic areas must be normal to exclude radiculopathy, or lower lumbar and sacral plexus infiltration or damage.
4. Surgical exploration of the proximal sciatic nerve should confirm an absence of mass lesions. Ideally, compression of the sciatic nerve by the piriformis muscle or associated fibrous bands should be identified. However, it can sometimes be difficult to recognize a compressed nerve [visually].
5. Relief of symptoms and improvement in neurological abnormalities should follow surgical decompression.

This set goes well beyond what one really needs. There are pretty clear vestiges of “diagnosis of exclusion” in criteria 3 and 4 (below), which have been discussed elsewhere:11

3. Paraspinal and pelvic muscle [needle] electromyography (EMG) must be normal to exclude a radiculopathy.
4. Surgical exploration should confirm an absence of mass lesions.

It is as though one defined a rectangle as “a quadrilateral with pairs of sides which are equal in length and which stay in one plane, having nothing but right angles,” whereas all that is needed is “a parallelogram with one right angle.” The second definition is much easier to prove. PS is entrapment of the sciatic nerve by the piriformis muscle. That is all. But, let us look at Stewart’s criteria more closely.

In research on PS, it is necessary to exclude other conditions that might confound outcome studies. But in clinical medicine, as in life, the situation can be more complex. One can have two things at the same time. Failure to exclude tuberculosis does not change the diagnosis of small cell carcinoma in a patient having difficulty breathing. Eczema may be confused with poison ivy, but does not exclude it.

The rest of Stewart’s set also errs on the side of conservatism: There is no real necessity for sciatic nerve damage as suggested in criterion 1 either. In carpal tunnel syndrome (CTS) and pronator syndrome, symptoms, such as paraesthesias and pain, and/or signs, such as weakness and sensory deficit (that are confirmed by NCV slowing and thereby are traceable to nerve compression), are sufficient for the diagnosis. That is the case here, too. There may be damage, and experience indicates there likely will be damage if the condition persists, but no proof of it is needed to diagnose CTS.

Relief of symptoms with surgery, criterion 5, as Dr. Stewart actually concedes in his article, is not essential to the diagnosis of any compression neuropathy. Neither is relief of symptoms with surgery essential to the diagnosis of cancer, fracture, or anything else. However, such relief might help determine which of several conditions is causing the patient’s symptoms.

The second part of criterion 4 is quite relevant to the subject under consideration here, since conductions that are tested in a provocative position are exactly intended to turn up pathology that is not structural, where there are no anatomical signs nor visible clinical changes. Dr. Stewart warns that this might be difficult in the second italicized sentence (italics and bracketed text added by the author for emphasis): “However, it can sometimes be difficult to recognize a compressed nerve.” Indeed, it might be nearly impossible, since the pathology is in the dynamic changes that occur with movement, and any motionless, conventional study, structural or electromyographic, in fact . . . almost any study, that fails to quantify the neurophysiological, functional changes that take place with changes in position, is almost certain to overlook. This assertion will be evaluated below.

Equally obvious is the only one of Dr. Stewart’s criteria that is left standing, number 2: “Presence of electrophysiological evidence of sciatic nerve damage,” and the fact that conventional needle EMG studies pick up only the most severe and egregious examples of PS, where compression had gone on long enough or progressed far enough to produce denervation.

More than 79% of the patients identified by the FAIR test recover at least 50% (visual analogue scale<50% original value) within 2-3 months if given via a needle EMG-guided Lidocaine or Marcaine and steroid injections, and within 2-3 weeks after botulinum injections, provided appropriate physical therapy follows the injection. Patients in a 1,014-leg study had suffered from sciatica for a mean 6.5 years previous to this author’s diagnosis and treatment.12 Clinical criteria for PS are sciatica, buttock pain, and buttock tenderness. Figure 3 illustrates how functional application of the H reflex in the FAIR test improves the ability to identify the piriformis pathology.

In this author’s treatment of PS, myofascial release and McKenzie exercises were used to free up the anterior and posterior divisions of lumbar roots in order to give the lumbosacral plexus and origins of the sciatic nerve more slack, which would, in turn, enable the sciatic nerve to respond to the pressure of a tightened piriformis muscle by moving aside. In a final impulse stemming from the “diagnosis of exclusion” mentality, Dr. Stewart criticized this treatment protocol for its nonspecificity, pointing out that myofascial release of the lumbosacral paraspinals would also treat a herniated nucleus pulposis, and reasoning that therefore the good results in patients with PS mean nothing. But giving a man steroids to treat eczema does not mitigate against its curing poison ivy, even if some people manage to have both.
However, his question did provoke a search for patients with magnetic resonance imaging (MRI) scans which found 440 patients, 320 (73%) of whom had at least one negative and no positive MRIs and 120 (27%) of whom had at least one positive MRI for lumbosacral pathology, such as a herniated disc or moderate-to-severe spinal stenosis.

Even before looking at the results, one may ask, would even 100% having positive lumbosacral pathology vitiate the significance of positive results? Unlike the 918 patients in this study had been seen an average of 6.5 clinicians prior to being entered in this study. By far, the majority had at least one documented course of physical therapy focused on the lumbar spine. The average FAIR test-positive patient had suffered for 6.2 years.

In fact the MRI positive and negative groups were quite similar in outcome, suggesting yet again what is already known: that one can have two diagnoses at the same time. The PS diagnosis just happened to contribute more to these patients’ symptoms than their other pathology (Table 1).

How Does Dual Diagnosis Affect Treatment?

Only two differences appeared between those with and those without positive MRIs and paraspinal needle EMGs. First, and more importantly, the 120 patients with positive MRIs took a mean full year longer to seek treatment for a second condition, PS. The “diagnosis of exclusion” attitude may have brought them an extra year of pain. Caregivers might have reasoned: “They have a herniated disc. Why search for other pathology (although they did not respond even to surgical intervention?).” At any rate, they endured 12 months of pain before someone, usually the patients themselves, looked further. Second, a slightly greater percentage of the group which had both negative MRI and negative needle EMG results improved 50% or more. Possibly a minor contribution of pain from the untreated spinal diagnosis in the MRI or needle EMG positive cases was responsible for this.

PART TWO: NEURAL SCANNING

Although other needle EMG techniques have appeared, another interesting development since 2003 is the application of neural scanning to the diagnosis of PS. Neural scans currently are the most effective way to image soft tissues such as nerves and muscles. Developed and championed by Dr. Aaron Filler, a neurosurgeon at Cedars-Sinai Hospital in Beverly Hills, California, neural scans essentially take a standard MRI image and then digitally subtract the fat-suppression image from the whole image:

- Normal image of the buttock
- Image of buttock without the fat
- Image of fatty structures of the buttock

The fatty myelin sheaths of peripheral nerves render them particularly prominent in the digitally-subtracted image. Incidentally, Dr. Filler’s work met a number of Dr. Stewart’s stringent requirements for identifying PS. In one paper he studied 239 people, approximately half of whom had undergone unsuccessful spinal surgery and the other half of whom had no conventional MRI evidence of spinal pathology. He used the...
neural scan to produce hundreds of different images of their spines, lumbosacral plexi, and pelves (Fig. 4).

Dr. Filler found 67% of these cases of “nondisc” sciatica to be due to PS, but also a small percentage due to far lateral disc herniations and spinal stenoses that were missed, and another 4% due to entrapment of the sciatic nerve at the ischial tunnel. A conventional needle EMG is likely to pick up paraspinal denervation in a far lateral disc herniation and spinal stenosis, but ischial tunnel syndrome versus PS is a distinction that currently only neural scanning is able to make.

Dr. Filler and colleagues went further. They noted that 1.2 million MRIs were performed in 2002 for sciatica, yet only 200,000 surgeries were performed. They concluded that nondisc sciatica may be as common or more common than herniated disc-caused sciatica. Fully two-thirds of these nondisc sciatica appeared to be PS.

Treatment for PS is persuasively successful. Many physicians’ (including this author’s) as well as Dr. Filler’s injection records encourage clinicians to regard PS as a diagnostic entity, since more than 79% of people diagnosed with PS and treated by any of these methods have had at least an extended period of relief.\textsuperscript{4,15,16} Surgical relief also has been the rule in the small minority of patients requiring it. In their reports, both Dr. Filler and other surgeons satisfy another of Dr. Stewart’s original criteria, finding denudation of the vaso nervorum and other changes in the flattened sciatic nerve precisely at its area of contact with the piriformis muscle.\textsuperscript{17,18}

Some have rejected Dr. Filler’s work on the basis of there being a conflict of interest in a researcher who has created his own corporation to use the results of his published work. Dr. Filler’s work was thus summarily dismissed in an evening meeting at the Hospital for Special Surgery in New York. But imputing motives, especially bad motives, is always sketchy business. One could not help thinking of another inventor with the same conflict, Thomas Edison, as this subject was discussed in the well-lit auditorium.

Physical therapy and yoga have helped the vast majority of PS patients. Most interesting is the striking correlation of sciatic-type pain versus FAIR test delay of the H reflex in serial testing during therapy (Fig. 5).

**PART THREE: FUNCTIONAL NEEDLE ELECTROMYOGRAPHY**

The third and last development that must be considered is expansion of the functional electrophysiological technique of the FAIR test to two other clinical problems.

Dynamic Assessment of Neurological Thoracic Outlet Syndrome
Electrophysiological confirmation of neurological thoracic outlet syndrome (TOS) has been sought, but results, generally focused on the ulnar nerve, and have been inconsistent at best.\textsuperscript{19-35} The pain and paraesthesias of TOS often are exacerbated by movements of the neck and shoulder. This has prompted some clinicians to attempt diagnosis with Adson’s maneuver and the Allen test, provocative maneuvers in which patients draw and hold a maximal breath after revolving their heads ipsilaterally and contralaterally, respectively, with proband arm both abducted and externally rotated 90 degrees. The test is positive if the radial pulse disappears with the maneuver, indicating that compression of the neurovascular bundle exceeds systolic blood pressure. This, of course, is a vascular indication of a neurological phenomenon, and, as such, is inherently imprecise.

Preliminary work in this author’s laboratory suggests that this provocative maneuver may help in electrophysiological assessment of TOS (Figs. 6, 7, and 8).

Comparing proximal motor latencies (PMLs) in the anatomical position with PMLs in Adson’s maneuver and especially Allen test positioning appears to reflect entrapment between the clavicle and the coracoid process. Surprisingly, these were most dramatically positive for the axillary nerve. There may be a straightforward anatomical/kinesiological reason for this (Table 2 and Fig. 6 legend).

But, the proof of the pudding lies in whether this electrophysiological test distinguishes a patient characteristic that can be meaningfully treated. Do these patients respond to treatment focused on the region to which the test directs the clinician’s attention?

Patient selection included a positive Adson’s maneuver or Allen test, a negative cervical MRI, and symptoms or signs that reliably changed with movement at the shoulder. The most typical symptoms were pain, paraesthesias, and/or perceived numbness. The peripheral nerve that was clinically most involved by virtue of sensory complaints and motor function was the one tested. In ambiguous cases, more than one nerve was tested, and the most positive one used in the study. Patients showing more than 1 ms delay in that nerve’s PML (2 standard deviations beyond the

<table>
<thead>
<tr>
<th>MRI</th>
<th>Number</th>
<th>Improved &gt;50% (%)</th>
<th>Mean improvement (%)</th>
<th>Years of pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>129</td>
<td>74.7</td>
<td>62.3</td>
<td>6.9</td>
</tr>
<tr>
<td>Negative</td>
<td>320</td>
<td>74</td>
<td>61.5</td>
<td>5.8</td>
</tr>
<tr>
<td>Negative MRI</td>
<td>179</td>
<td>76</td>
<td>61.8</td>
<td>5.9</td>
</tr>
<tr>
<td>Negative EMG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Magnetic resonance imaging of patients with positive FAIR test (n=449)

Whether or not the magnetic resonance imaging scans were positive for spinal pathology, the treatment of injection and physical therapy for patients with positive FAIR tests was equally effective. The same held for the results of conventional electrodiagnostic studies.

EMG = electromyography, FAIR = flexion, adduction, and internal rotation, MRI = magnetic resonance imaging
Table 2. The average PML delay induced by the Allen test in selected patients was more than 3 standard deviations (SD) beyond the mean found in normal subjects; the SD of that delay was quite close to the SD of the PML in the anatomical position.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Anatomical</th>
<th>Adson’s test</th>
<th>Delay</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillary nerve</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3.7</td>
<td>6.0</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4.2</td>
<td>5.7</td>
<td>1.5</td>
<td>Lupus</td>
</tr>
<tr>
<td>3</td>
<td>4.1</td>
<td>5.4</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4.5</td>
<td>7.8</td>
<td>3.3</td>
<td>Lupus</td>
</tr>
<tr>
<td>5</td>
<td>4.1</td>
<td>6.3</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4.3</td>
<td>6.1</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3.8</td>
<td>5.2</td>
<td>1.8</td>
<td>Football “zinger”</td>
</tr>
<tr>
<td>8</td>
<td>3.8</td>
<td>5.2</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4.7</td>
<td>6.5</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>5.9</td>
<td>7.5</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>4.4</td>
<td>4.8</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>4.9</td>
<td>6.6</td>
<td>1.66</td>
<td>Morbidly obese</td>
</tr>
<tr>
<td>Radial nerve</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>1.9</td>
<td>3.0</td>
<td>1.1</td>
<td>Snapping scapula</td>
</tr>
<tr>
<td>14</td>
<td>3.1</td>
<td>4.8</td>
<td>1.7</td>
<td>63-year-old skier</td>
</tr>
<tr>
<td>15</td>
<td>3.6</td>
<td>5.3</td>
<td>1.7</td>
<td>Fall</td>
</tr>
<tr>
<td>16</td>
<td>3.7</td>
<td>6.0</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>3.8</td>
<td>6.7</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>26.9</td>
<td>28.3</td>
<td>1.4</td>
<td>F wave</td>
</tr>
<tr>
<td>19</td>
<td>12.0</td>
<td>13.6</td>
<td>1.6</td>
<td>Postmastectomy</td>
</tr>
<tr>
<td>20</td>
<td>2.4</td>
<td>5.6</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Musculocutaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>5.4</td>
<td>6.9</td>
<td>1.8</td>
<td>Fall</td>
</tr>
<tr>
<td>22</td>
<td>23.1</td>
<td>25.0</td>
<td>1.5</td>
<td>Sensory loss</td>
</tr>
<tr>
<td>23</td>
<td>28.3</td>
<td>30.0</td>
<td>1.7</td>
<td>F wave</td>
</tr>
<tr>
<td>24</td>
<td>27.5</td>
<td>29.6</td>
<td>2.1</td>
<td>F wave</td>
</tr>
<tr>
<td>Ulnar</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>7.7</td>
<td>9.6</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>28.3</td>
<td>30.0</td>
<td>1.7</td>
<td>F wave</td>
</tr>
<tr>
<td>27</td>
<td>27.5</td>
<td>29.6</td>
<td>2.1</td>
<td>F wave</td>
</tr>
<tr>
<td>Suprascapular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>7.0</td>
<td>9.1</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>26.1</td>
<td>27.6</td>
<td>1.5</td>
<td>F wave</td>
</tr>
<tr>
<td>30</td>
<td>27.7</td>
<td>29.1</td>
<td>1.4</td>
<td>F wave</td>
</tr>
<tr>
<td>Thoracodorsal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>3.8</td>
<td>6.1</td>
<td>2.3</td>
<td></td>
</tr>
</tbody>
</table>

Average delay | 1.731 |
Standard deviation | 0.543 |

PML = proximal motor latency
maximal normal value\textsuperscript{4}) were treated and serially tested every 2 weeks for 12 weeks. The study was approved by the Sound Shore Medical Center Institutional Review Board.

Two groups of patients received 2,500 and 5,000 units of botulinum neurotoxin type B (BT-B) injection into the scalenus anticus and medius (two locations in each muscle) as well as physical therapy consisting of myofascial work, scapular kinetics, and a figure-of-eight brace. Control patients were given physical therapy, and a brace, but no injection. There was significantly greater benefit for those patients receiving injections (Fig. 9).

The patients satisfied another criticism that the initial piriformis work sustained: because the physical therapy for PS involved work in the paraspinal region, it was speculated that the therapy would help people with spinal causes of sciatica, and therefore patient improvement was not a reliable indicator of PS. In patients with TOS the physical therapy was plainly helpful, but injections into the scalenii would be of value in TOS, but not cervical pathology.

Distinguishing Spinal Stenosis from Radiculopathy When Both Occur at the Same Level: Which is the Main Pain Generator?

Intraspinal Stenosis Versus Foraminal Stenosis

So far this discussion has reviewed two attempts to adopt operational definitions of “diagnoses of exclusion.” Objective criteria was sought for TOS and PS. This final example of functional needle EMG represents an attempt to determine which of two co-present diagnoses is the one that matters. This is needed when a patient has two diagnoses with similar symptoms but dissimilar treatments. That situation frequently involves a herniated disc and associated spinal stenosis. It is not rare to have these two diagnoses joined by spondylolisthesis, either. Unfortunately, from a therapeutic point of view, they are opposites. The best treatment for spinal stenosis and spondylolisthesis takes place in flexion, and these conditions are worsened by extension, while herniated nucleus pulposus most often responds to extension, and is frequently exacerbated by flexion. Because the two occur together in a fair number of cases, the therapeutic community regularly faces the options of either treating one condition while exacerbating the other, or doing nothing at all. These unpleasant alternatives can only be avoided by determining which of the two conditions is the more troubling, which of the two conditions is the primary pain generator.

Functional needle EMG may exploit the neuroskeletal changes brought about by flexion and extension. Any consistent electrophysiological changes will reflect neurological consequences of the structural changes that positional variations bring about in herniated spinal discs and stenoses. Because the course of the H reflex traverses the entire lumbar spine, and is replicable under normal conditions, it is a fair vehicle to carry these changes. The idea is to determine the changes in the H reflex from flexion and extension, as compared to the anatomical condition. This may not be too far-fetched, since extension has been noted to further narrow the stenotic intraspinal canal by up to 63\%\textsuperscript{37,38} while the
herniated portion of a lumbar disc described by McKenzie and colleagues retract during extension, further opening neuroforamina.39

If electrophysiological investigations are extensions of the physical examination, then provocative maneuvers such as extension and flexion might well have electrodiagnostic correlates. These seem to be the conditions in which one may reliably evoke them.

Some maneuvers are not exactly provocative. Terming something “provocative” insinuates that its effects are more or less unpleasant, while some maneuvers, such as the Jendrassic maneuver, enhance normal responses. It might be better to call this type of maneuver “evocative.” As a case in point, extension may reduce foraminal disease due to disc herniation. Extension may reduce H-reflex latency and enhance its amplitude, even making visible a previously undetectable response. For foraminal narrowing, extension may be an evocative maneuver, while flexion may be provocative, and worsen conduction parameters. For spinal stenosis, flexion may evoke a previously absent H reflex and F wave or enhance the amplitude or diminish the latency of a preexisting one, while extension may provoke just the reverse.4

Dr. Allen Wilkins and I have recently completed a book on this subject, calling it positionally exacerbated spinal stenosis and the reader is referred to it for greater detail.11 We worked only with the provocative nature of spinal extension. Here, it is perhaps adequate to note that comparing the H reflex in the anatomical position with a series of H reflexes obtained over a 3-min period during which the patient is in extension shows how the position has provoked significant delay in the H reflex (Fig. 10). The delay generally appears after 2.5 min have elapsed. More important,

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>MRI</th>
<th>Needle EMG</th>
<th>Anatomical</th>
<th>3-min extension</th>
<th>Contralateral</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>41</td>
<td>Severe central and left lateral recess stenosis</td>
<td>Denervation left L5-S1-S2</td>
<td>28.4</td>
<td>31.3</td>
<td>23.7</td>
<td>Left posterior tibialis H reflex used increased pain with extension LBP, hip and buttck pain LBP</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>70</td>
<td>Stenosis</td>
<td>Denervation S1-2</td>
<td>37.1</td>
<td>39.4</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>80</td>
<td>Stenosis</td>
<td>Denervation S1-2</td>
<td>33.74</td>
<td>34.1</td>
<td>34.9</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>72</td>
<td>Stenosis</td>
<td>Normal</td>
<td>43</td>
<td>44.6</td>
<td>41.8</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>79</td>
<td>Stenosis, L3-4 by CT</td>
<td>Bilateral L3-4-5-S1, chiefly L5-S1</td>
<td>35.9</td>
<td>39.6</td>
<td>35.9</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>40</td>
<td>Stenosis</td>
<td>Left L4-5-S1; right L5</td>
<td>35.1</td>
<td>36.7</td>
<td>32.5</td>
<td>Pain increased with walking LBP</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>76</td>
<td>Stenosis, S/P surgery</td>
<td>Normal</td>
<td>41.7</td>
<td>43.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>45</td>
<td>Mild/moderate L3-4 stenosis</td>
<td>2.1 ms delay in FAIR-position</td>
<td>36.81</td>
<td>37.9</td>
<td>34.2</td>
<td>Bilateral electric shocks with heel strike and continuous bilateral sciatica LBP, numbness left dorsal foot, lateral calf</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>80</td>
<td>Stenosis, three surgeries</td>
<td>Bilateral L4-5</td>
<td>37.6</td>
<td>39.7</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>54</td>
<td>Stenosis</td>
<td>Bilateral L5-S1, left posterior tibialis</td>
<td>34.3</td>
<td>37.4</td>
<td>34.7</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>44</td>
<td>Grade I spondylolisthesis stenosis; became grade II in 7 months</td>
<td>Normal at first, 7 months later bilateral denervation L5-S1</td>
<td>32.4</td>
<td>32.9</td>
<td>33</td>
<td>LBP left more than right; eventually had surgery Lumbar eburnation and pain with extension Left sciatica, foot drop</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>62</td>
<td>Stenosis</td>
<td>Normal</td>
<td>39.6</td>
<td>41.1</td>
<td>34.7</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>53</td>
<td>Stenosis</td>
<td>Vastus medialis, gastrocnemius, anterior tibialis</td>
<td>34.7</td>
<td>36.6</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>4 males</td>
<td>61.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard deviation</td>
<td>15.7</td>
<td>3.9</td>
<td>3.9</td>
<td>2.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CT = computed tomography, EMG = electromyography, LBP = low back pain, MRI = magnetic resonance imaging, S/P = status post

Table 3. Three minutes in maximal extension prolonged these patients’ H reflex. Serial testing usually began to display the delay late in this period, often after 2.5 minutes.
treating these patients in physical therapy according to whether there has been a significant delay with extension (spinal stenosis) or not (neuroforaminal stenosis) has led to amelioration of their symptoms. Because these patients’ outcome was better than those treated without thus identifying the main pain generator, it suggested that the extension maneuver was worth the effort (Tables 3, 4, and 5).

There are other conditions that have responded to functional maneuvers with electrophysiological changes. Subtle or incipient CTS and subclinical pronator syndrome are examples of conditions in which provocative maneuvers can determine the causes of pain before they bring about structural damage. Looking for significant differences between electrophysiological metrics elicited in anatomical and provocative-positions requires finding side-to-side standard deviations. If the anatomical-to-provocative change is beyond 2 standard deviations from the mean side-to-side variation, then the value likely is significant. After all, the differences between one limb and its counterpart can hardly be less than the difference between a limb and itself.

### CRITICAL SUMMARY

Functional maneuvers appear to reveal position- or movement-related pathology. Evidence supporting this includes imaging studies and positive results from treatment directed to the site of the indicated pathology. But, there has been no standardization of position, forces applied, or their duration. Before techniques such as these can be fully accepted further studies are needed.

### REFERENCES


Piriformis Syndrome is Overdiagnosed

Robert Werner, MD, MS
Chief, Physical Medicine and Rehabilitation
Veterans Administration Medical Center
University of Michigan Health System
Ann Arbor, Michigan

INTRODUCTION

There is a great deal of controversy regarding the existence of piriformis syndrome (PS). Although not listed in Dorland's Medical Dictionary or many medical encyclopedias, the National Institute of Neurologic Disorders and Stroke within the National Institutes of Health defines the syndrome as “a rare neuromuscular disorder that occurs when the piriformis muscle compresses or irritates the sciatic nerve.” If one accepts the diagnosis as real, confusion reigns over how to establish it. PS most often is referred to as a form of sciatic nerve entrapment causing buttock and hamstring pain. The original description of this condition dates from 1928 when Yeoman stated that “insufficient attention” has been paid to the piriformis muscle as a potential cause of sciatica.1 Despite this, Sunderland never mentions PS in his review of the causes of sciatic nerve injury.2 He reported that only 1.5% of all cases in his series of 209 cases were caused by compression (Table) and he did not attribute any of these to PS. Similarly, a review of the last 5 years at this author’s electrodiagnostic (EDX) laboratory found 96 cases of sciatic neuropathy and none were attributed to PS.

When searching Medline, PS is not listed as a medical subject heading. Similar compression neuropathy “syndromes” such as thoracic outlet syndrome (TOS) and carpal tunnel syndrome (CTS) have accepted medical subject headings. The lack of a consensus definition of PS and the fact that PS is not mentioned in many prominent textbooks such as The Essentials of Musculoskeletal Care3 by the American Society of Orthopaedic Surgeons and Sunderland’s Peripheral Nerves and Nerve Injury2 are a strong indication that the medical community has not embraced the term.

Assuming the syndrome does exist, the lack of testing or imaging to help establish a diagnosis makes it difficult to determine the prevalence of the disorder.4 It is a syndrome and is defined based upon the history and clinical presentation. Most efforts at confirming the diagnosis have not been helpful. If the syndrome involves an abnormality of the sciatic nerve as it passes by the piriformis muscle, physicians should be able to identify an abnormality of the sciatic nerve using electrophysiologic measures or demonstrate an abnormality on imaging studies. Stewart suggested the following criteria for establishing the diagnosis of PS:5

- Symptoms and signs of sciatic nerve damage must be present.
- Electrophysiological evidence of sciatic nerve damage must be present. Paraspinal muscle needle electromyography (EMG) must be normal, to help exclude a radiculopathy.
- Imaging of the lumbosacral nerve roots and of the paravertebral and pelvic areas must be normal (to exclude radiculopathy) or lower lumbar or sacral plexus infiltration or damage. Imaging of the pelvis and sciatic notch must show the absence of mass lesions there.
- Surgical exploration of the proximal sciatic nerve should confirm an absence of mass lesions. Ideally, compression of the sciatic nerve by the piriformis muscle or associated fibrous bands should be identified. However, it sometimes can be difficult to recognize a compressed nerve.
- Relief of symptoms and improvement in neurological abnormalities should follow surgical decompression. As in other situations of chronic nerve damage, decompression may not always lead to symptom relief. Surprisingly, surgical division of the piriformis muscle has been described as relieving pain in patients with lumbosacral radiculopathies.
the condition be confirmed? If those patients with buttock pain reports pain from nerve irritation, there are typically sensory fiber damage. In most compressive neuropathies, if the patient do not meet the criteria for PS. The exclusion of these patients do not meet the criteria for PS. If the symptoms are a result of buttock trauma, radicular involvement and plexus involvement does not establish the diagnosis of PS. If the pain is caused by injections into the piriformis muscle and sciatic notch area the report of pain relief following local anesthetic or corticosteroid injections into the piriformis muscle and sciatic notch area does not establish the diagnosis of PS. If the pain is caused by a strain or post-traumatic scarring of the piriformis muscle, injections will tend to relieve local symptoms, but this does not imply that the sciatic nerve was involved in generating the pain. Additionally, it is recognized that a nerve block distal to a nerve lesion can still provide pain relief. One study even found that division of the piriformis muscle in patients with lumbosacral radiculopathy, pelvic muscle strain, tumors or other masses at the sciatic notch, as well as post-traumatic scarring in this area. Tenderness may indicate an abnormality of the piriformis muscle, but it does not mean that the sciatic nerve is injured.

Establishing the diagnosis of PS rests upon excluding other disorders that have overlapping symptoms and then using provocative maneuvers to demonstrate irritation of the sciatic nerve when the piriformis muscle is either contracted or stretched. The validity of these signs is suspect as is the claim that they are specific for demonstrating compression of the sciatic nerve by the piriformis muscle. Similar to Tinel’s and Phalen’s signs for CTS, and Adson’s maneuver for TOS, the sensitivity and specificity of these provocative tests is quite poor. The provocative tests for PS have not been critically evaluated. Tenderness with deep palpation in the buttock is common in patients with lumbosacral radiculopathy, pelvic muscle strain, tumors or other masses at the sciatic notch, as well as post-traumatic scarring in this area. Tenderness may indicate an abnormality of the piriformis muscle, but it does not mean that the sciatic nerve is injured.

The report of pain relief following local anesthetic or corticosteroid injections into the piriformis muscle and sciatic notch area does not establish the diagnosis of PS. If the pain is caused by a strain or post-traumatic scarring of the piriformis muscle, injections will tend to relieve local symptoms, but this does not imply that the sciatic nerve was involved in generating the pain. Additionally, it is recognized that a nerve block distal to a nerve lesion can still provide pain relief. One study even found that division of the piriformis muscle in patients with lumbosacral radiculopathy, pelvic muscle strain, tumors or other masses at the sciatic notch, as well as post-traumatic scarring in this area. Tenderness may indicate an abnormality of the piriformis muscle, but it does not mean that the sciatic nerve is injured.

The majority of the reports of PS do not demonstrate objective evidence of sciatic nerve injury that is confirmed with EDX testing or imaging studies. This leaves the largest group of patients with complaints of chronic buttock pain but no evidence of sciatic nerve involvement. Is this really PS? Because sciatica is a vague term that includes many etiologies, it is only by a process of exclusion that PS could be considered. If the primary symptom is buttock pain (often with sciatica) and no neurological deficits are found, PS is one of many possible causes. The exclusion of radicular involvement and plexus involvement does not establish the diagnosis of PS. If the symptoms are a result of buttock trauma, these patients do not meet the criteria for PS.

The main issue is whether PS actually causes compression of the sciatic nerve with resultant pain but no evidence of nerve fiber damage. In most compressive neuropathies, if the patient reports pain from nerve irritation, there are typically sensory or motor symptoms, clinical deficits, and electrophysiological abnormalities. If the nerve injury cannot be documented, can the condition be confirmed? If those patients with buttock pain also have complaints of sciatica, it should be recognized that the term sciatica may mean different things to different people and the causes of sciatica can be quite varied. Most would accept a definition for this term as being pain radiating down the leg from the lower back, buttock, or hip. Despite the terminology, the definition does not indicate sciatic nerve involvement. The most frequent neurological etiology is a lumbosacral radiculopathy, but lumbar and sacral plexopathy and proximal sciatic neuropathies are also common. It also is likely that they cause a musculoskeletal abnormality of the lumbosacral spine, hip, or pelvis. There may be a tendonitis of the piriformis muscle itself due to over activity (usually sports-related) without any involvement of the sciatic nerve. This type of pain, in the buttock and the posterior thigh, is common and frequently described by patients and healthcare providers as sciatica despite no neurologic injury.

Table. Causes of sciatic nerve injury

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stab wound</td>
<td>1%</td>
</tr>
<tr>
<td>Ganglia or tumor</td>
<td>0.5%</td>
</tr>
<tr>
<td>Gunshot wound</td>
<td>70%</td>
</tr>
<tr>
<td>Iatrogenic during surgery</td>
<td>1.5%</td>
</tr>
<tr>
<td>Compression</td>
<td>1.5%</td>
</tr>
<tr>
<td>Injection injury</td>
<td>3%</td>
</tr>
<tr>
<td>Dislocation of hip</td>
<td>9%</td>
</tr>
<tr>
<td>Fracture of acetabulum</td>
<td>2.4%</td>
</tr>
<tr>
<td>Fracture of femur</td>
<td>5.3%</td>
</tr>
<tr>
<td>Injury of the knee with traction</td>
<td>5.3%</td>
</tr>
</tbody>
</table>

From Sunderland; a series of 209 cases with peripheral nerve injury.
this since none of the cases of identified sciatic nerve injury at the EMG laboratory (n=96) were suspected to have PS.

There is one novel electrophysiologic study associated with a provocative technique that supported the contention that there was objective evidence of sciatic nerve involvement in a high percentage of patients with disputed PS where traditional electrophysiologic studies and radiographic studies had been normal. Fishman and colleagues reported a series of 918 patients with disputed PS. The entry criteria for disputed PS consisted of nonspecific symptoms and signs. Their exclusion criteria were not described. They did not perform the standard electrophysiologic studies of sciatic nerve function but instead used an H-reflex testing protocol before and after a provocative posture (hip flexion, adduction, and internal rotation). The H-reflex testing protocol has not been reproduced in other EMG laboratories and even when performed by Fishman it has a reported 35% false-positive rate in normal control subjects. This is analogous to the high false-positive rate for Adson’s maneuver in the evaluation of TOS. Fishman and colleagues also evaluated treatments which were broad-based and had the potential to provide benefit to patients with a wide variety of musculoskeletal disorders of the lower spine, pelvis, and hips. Most patients in the study improved regardless of how many clinical criteria they met or whether the H-reflex test was abnormal. The lack of reproducibility and the high false-positive rate of the provocative H-reflex protocol make this study of questionable value in establishing the diagnosis of true neurogenic PS.

SUMMARY

The medical community is uncertain whether there is an entity called PS. There are certainly patients with unexplained buttock pain but no consensus as to how to use the term PS. McCrory has written: “Whether the piriformis muscle is the cause of the compression has not been clearly established. It is possible that the obturator internus/gemelli complex is an alternative cause of neural compression. For this reason, I suggest that sports medicine clinicians consider using the term ‘deep gluteal syndrome’ rather than piriformis syndrome.” This assumes that some type of nerve compression is involved, which is debatable, since there are many musculoskeletal disorders that can mimic the symptoms. Given this overlap of symptoms, there will be many clinicians who choose to lump these disorders into one term. If this is the case, this author believes a classification system of true neurogenic PS should be adopted to help distinguish the cases where there is objective electrophysiologic evidence of localized sciatic nerve involvement from the vast majority of cases in which there is only vague symptoms. Response to treatment that is focused on injection into the piriformis muscle with subsequent relief of symptoms is not a diagnostic confirmation of PS. Muscle strain or posttraumatic scarring treated with massage or injection is a different entity than that proposed by Yeoman in the 1920s.

Physicians need to differentiate a disorder of the muscle from that of a compression neuropathy. If it cannot be done, physicians need to be honest and use a term such as “disputed PS” or “disputed deep gluteal syndrome” to reflect the true status of medicine’s understanding of these patients. Alternatively, local muscle and tendon disorders that do not involve the sciatic nerve need to be redefined. If the buttock pain is referred from the lumbosacral spine or pelvis, the term PS is discouraged. In many patients a diligent search for alternative causes of their pain can prove helpful.

REFERENCES

Crossfires: Piriformis Syndrome, Thoracic Outlet Syndrome, and Tarsal Tunnel Syndrome
CME Questions

1. True neurogenic thoracic outlet syndrome is often associated with all of the following EXCEPT:
   A. Intrinsic hand muscle weakness and atrophy.
   B. Numbness over the medial (ulnar) side of the hand and arm.
   C. Neck pain.
   D. A cervical rib.

2. Electrophysiologic findings in true neurogenic thoracic outlet syndrome may include all of the following EXCEPT:
   A. Fibrillation potentials on needle electromyography in the abductor pollicis brevis and abductor digiti minimi muscles.
   B. Absent median sensory nerve action potentials.
   C. Low amplitude median and ulnar compound motor action potentials.
   D. Absent or reduced medial antebrachial cutaneous sensory nerve action potentials.

3. There is high quality, randomized, controlled trial evidence to support which of the following treatments in the disputed form of thoracic outlet syndrome?
   A. Conservative therapy with a tailored exercise program.
   B. Corticosteroid therapy.
   C. Surgical decompression by any method.
   D. Acupuncture.
   E. None are correct.

4. Why do many physicians believe that the disputed form of neurogenic thoracic outlet syndrome is over-diagnosed?
   A. There are no objective abnormalities on neurologic examination.
   B. There are no abnormalities on the electrophysiologic studies.
   C. There is no high quality evidence that surgical decompression is effective.
   D. It commonly is seen in the setting of personal injury litigation.
   E. All are correct.

5. All of the following statements regarding neurogenic thoracic outlet syndrome (NTOS) are true EXCEPT:
   A. The vast majority of such patients have suffered a prior head or neck injury or have a repetitive upper extremity positional stress.
   B. Classic provocative testing (Adson, Wright, military brace) plays a crucial role in establishing the diagnosis of NTOS.
   C. Vascular laboratory assessment of NTOS has reasonable sensitivity but a low specificity for the condition.
   D. A hallmark feature of patients with NTOS is that they inexorably worsen notwithstanding rest, appropriate physical therapy, and the passage of time.

6. All of the following statements regarding electrodiagnostic (EDX) testing for neurogenic thoracic outlet syndrome (NTOS) are true EXCEPT:
   A. EDX is a central part of the diagnosis of true or classic NTOS (e.g. following gunshot or stab wound to the brachial plexus).
   B. EDX is positive in nonspecific NTOS only in the presence of concurrent cervical radiculopathy or peripheral nerve compression (e.g. carpal or cubital tunnel syndrome).
   C. Short-latency somatosensory evoked potential and single-fiber testing are useful in the diagnosis of both true and nonspecific NTOS.
   D. Median antebrachial cutaneous nerve conduction delay is commonly positive in nonspecific NTOS.

7. Patients with nonspecific NTOS:
   A. Uncommonly experience headache.
   B. Have a predominant ulnar nerve distribution of numbness and tingling in the affected upper extremity.
   C. Often risk the development of intrinsic hand muscle atrophy.
   D. Frequently find they can relieve their upper extremity symptoms by abducting the arm.
8. Which is the best answer regarding intrascalene injections for NTOS?
   A. A significant exacerbation of symptoms supports the diagnosis of NTOS.
   B. A positive response to scalene block lacks adequate sensitivity and specificity for the diagnosis of NTOS.
   C. A positive response to scalene block underscores our current understanding of the pathophysiology of NTOS.
   D. A negative response to intrascalene Botox rules out the diagnosis of NTOS.

9. Each of the following statements about NTOS is true EXCEPT:
   A. EDX testing is sensitive and specific for the presence of nonspecific NTOS.
   B. Trauma to the head and neck, such as cervical hyperextension injuries in car accidents, are a common antecedent in NTOS.
   C. The careful exclusion of alternative diagnoses -- cervical spine, shoulder, peripheral nerve compression, fibromyalgia -- is central to the diagnosis of NTOS.
   D. No randomized trial of conservative or observational therapy for NTOS has been accomplished.

10. The diagnosis of NTOS in a motor vehicle accident victim is NOT supported by which of the following:
    A. Worsening of symptoms with the affected arm out-front or overhead.
    B. A positive ipsilateral scalene block with local anesthetic.
    C. A negative or non-diagnostic EDX battery.
    D. Immediate onset of symptoms following the motor vehicle accident.

11. The clinical differential diagnosis of tarsal tunnel syndrome (TTS) includes all of the following EXCEPT:
    A. Plantar fasciitis.
    B. Peripheral neuropathy.
    C. L5-S1 radiculopathy.
    D. Proximal tibial neuropathy.
    E. Peripheral vascular disease.

12. The most common cause of TTS is:
    A. Ganglion or schwannoma.
    B. Tenosynovitis.
    C. Trauma.
    D. Diabetic neuropathy.
    E. Rheumatoid arthritis.

13. Motor, sensory, and mixed nerve conduction studies (NCSs), along with needle EMG, can assist confirming the diagnosis of TTS in up to 90% of cases.
    A. True.
    B. False.

14. For the diagnosis of TTS, sensory or mixed NCSs are much more sensitive than the motor NCSs.
    A. True.
    B. False.

15. TTS is the most common entrapment neuropathy of the tibial nerve.
    A. True.
    B. False.

16. The treatment of TTS includes all EXCEPT.
    A. Nonsteroidal anti-inflammatory drugs.
    B. Corticosteroid injection.
    C. Epidural steroid injection.
    D. Corrective orthosis.
    E. Surgical decompression of the tibial nerve at the ankle.

17. AANEM 2005 guidelines stipulate that the following tests be performed to confirm the diagnosis of TTS EXCEPT:
    A. Tibial motor nerve conduction.
    B. Medial and lateral plantar sensory nerve conduction.
    C. Medial and lateral plantar mixed nerve conduction.
    D. Needle EMG of the tibial innervated foot muscles.

18. The differential diagnosis of TTS includes all of the following EXCEPT:
    A. Plantar fasciitis.
    B. Distal sensory polyneuropathy.
    C. L5 radiculopathy.
    D. Morton’s neuroma.

19. The signs and symptoms of TTS include which of the following?
    A. Weakness of ankle dorsiflexion.
    B. Sensory loss on the plantar surface of the foot.
    C. Atrophy of the extensor digitorum brevis muscle.
    D. Positive Tinel’s sign just behind the lateral malleolus.

20. Which of the following EDX techniques has the LOWEST sensitivity for detecting TTS?
    A. Prolongation of the tibial distal motor latency.
    B. Slowing of the medial plantar sensory nerve conduction velocity (NCV).
    C. Slowing of the calcaneal NCV.
    D. Prolongation of the medial plantar mixed nerve peak latency.

21. The treatment of tarsal tunnel syndrome includes all of the following EXCEPT:
    A. Tarsal tunnel release.
    B. Gabapentin.
    C. Corticosteroid injections.
    D. Ultrasound treatment.

22. What is a clinical definition of piriformis syndrome?
    A. Pain in buttock, tenderness in buttock, and negative MRI of lumbar spine.
    B. Pain in buttock, tenderness in buttock, and sciatica.
    C. Pain in buttock, tenderness in buttock, and negative EMG of lumbar spine.
    D. A and B.
    E. A and C.
23. What is the electrodiagnostic finding in piriformis syndrome?
   A. Delay of the H-reflex in flexion, adduction, and internal rotation (FAIR-test).
   B. Delay of the F-wave in flexion, adduction, and internal rotation (FAIR-test).
   C. Delay of the H-reflex in flexion, adduction, internal rotation (FAIR-test), and negative spinal magnetic resonance imaging (MRI).
   D. Delay of the H-reflex in flexion, adduction, internal rotation (FAIR-test), and negative paraspinal EMG.
   E. None of the above.

24. A diagnosis of exclusion necessarily:
   A. Is overdiagnosed.
   B. Leads to misdiagnosis.
   C. Is insufficiently defined as a clinical entity.
   D. Is underdiagnosed.
   E. C and D.

25. NTOS:
   A. Historically has fairly unanimous electrodiagnostic criteria.
   B. Is indistinct from the vascular syndrome.
   C. May be induced by Adson’s maneuver.
   D. May be brought out by the Allen test.
   E. Is usually due to anatomical variation such as cervical rib.

26. Functional EMG:
   A. Only applies to piriformis syndrome.
   B. Is subjective.
   C. Needs more study to be standardized.
   D. Is an offshoot of functional MRI.
   E. Is illegal in the United States and Canada.

27. Stewart suggested criteria for establishing the diagnosis of piriformis syndrome and includes all of the following except:
   A. Presence of symptoms and signs of sciatic nerve damage.
   B. Presence of electrophysiologic evidence of sciatic nerve damage. Paraspinal muscle electromyography (EMG) must be normal to help exclude a radiculopathy.
   C. Imaging of the lumbosacral nerve roots and of the paravertebral and pelvic areas must be normal to exclude radiculopathy or lower lumbar or sacral plexus infiltration or damage.
   D. Surgical exploration of the proximal sciatic nerve should confirm an absence of mass lesions.
   E. Relief of symptoms and improvement in neurological abnormalities should follow botulinum toxin injection.

28. There is strong consensus on the definition of piriformis syndrome.
   A. True.
   B. False.

29. Electrodiagnostic testing can rarely confirm evidence of sciatic nerve injury with piriformis syndrome.
   A. True.
   B. False.

30. A provocative posture (hip flexion, adduction, and internal rotation) can be used to demonstrate a change in the tibial F wave in many patients with piriformis syndrome.
   A. True.
   B. False.