OVERVIEW OF WEAKNESS

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DIFFERENTIAL DIAGNOSIS OF WEAKNESS

Weakness has many causes, both neurological and non-neurological. Non-neurological causes of weakness include metabolic disturbances due to endocrine or electrolyte abnormalities; systemic illnesses of infectious, immunologic and neoplastic origin; and musculoskeletal disorders. Neurological causes of weakness may be divided into two broad categories: upper motor neuron disorders and the neuromuscular diseases.

The neuromuscular diseases are, in a broad sense, diseases of the motor unit which all produce symptoms of weakness. By convention, the neuromuscular diseases are divided into four nosologic groups: 1) anterior horn cell diseases, 2) peripheral neuropathies, 3) neuromuscular junction disorders, and 4) myopathies.

ANTERIOR HORN CELL DISEASES

Anterior horn cell diseases, also known as motor neuron diseases, are a group of disorders characterized by selective deterioration of motor neurons. Two major forms exist: a) spinal muscular atrophy, in which the involvement is exclusively of lower motor neurons, and b) amyotrophic lateral sclerosis, in which both upper and lower motor neurons are involved. Some authors include lateral sclerosis, a disease of upper motor neurons exclusively, under the category of motor neuron diseases, but others consider this disorder to be a form of multiple sclerosis. Table 1 lists the spectrum of motor neuron diseases.

<table>
<thead>
<tr>
<th>LMN Signs</th>
<th>LMN &amp; UMN Signs</th>
<th>UMN Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Muscular Atrophy</td>
<td>Amyotrophic Lateral Sclerosis (Motor Neuron Disease)</td>
<td>Lateral Sclerosis</td>
</tr>
<tr>
<td>- Infantile (Werdig-Hoffman)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Intermediate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Juvenile (Kugelberg-Welander)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Adult (Aran-Duchenne)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal muscular atrophies:</td>
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</tbody>
</table>

The spinal muscular atrophies are a group of motor neuron diseases characterized by degeneration of anterior horn cells and some cranial motor nerve nuclei, that results in progressive, generalized weakness of limb, trunk and bulbar musculature, muscular atrophy, fasciculations and hyporeflexia. These disorders involve primarily infants and children, and all tend to be autosomal recessive in inheritance. Recently, the abnormal
gene responsible for the childhood forms for spinal muscular atrophy has been localized to chromosome 5. The infantile form is rapidly progressive, with death occurring at the age of 2-3 years from respiratory failure. The intermediate and juvenile forms progress slowly and many patients live into adulthood.

**Amyotrophic lateral sclerosis (ALS):**

ALS is a progressive disorder of unknown etiology, characterized by degeneration of upper motor neurons, certain cranial nerve nuclei, and anterior horn cells, that results in diffuse muscle weakness and wasting, spasticity, hyperreflexia and bulbar (swallowing and speaking) dysfunction. ALS typically affects older individuals, with a median age of onset of 66 years. The disease is usually sporadic, although 5-10% of patients have a positive family history.

The diagnosis of ALS can be made with some assurance if weakness, wasting, fasciculations and hyperreflexia are found in three or more limbs. If dysphagia and dysarthria are also present, the diagnosis is even more likely.

Many patients with ALS develop a "pseudobulbar affect", which is a difficulty in controlling one's emotions.

The clinical course of ALS is progressive, and most patients die within three years of diagnosis due to respiratory failure.

The etiology of ALS is unknown. Recent lines of evidence support genetic factors in familial ALS (dysfunction of the enzyme superoxide dismutase on chromosome 19), excitotoxins such as glutamate, autoimmune processes, and accelerated neuronal degeneration.

Certain other illnesses with far better prognoses may mimic some of the signs and symptoms of ALS, and should always be considered in the differential diagnosis. Cervical spine disease, with spinal cord compression leading to upper motor neuron signs in the legs, and nerve root compression leading to lower motor neuron signs in the arms, needs to be ruled out. MR imaging of the cervical spine should therefore be obtained in all questionable cases.

There is no proven cure for ALS. Standard treatment consists of providing emotional support and coordinating symptomatic care including physical therapy, vigorous pulmonary toilet, and pharmacologic treatment of muscle spasticity, muscle cramps and depression.

**Riluzole**, an anti-glutamate agent, is the first specific treatment for ALS. This drug slowed the progression of ALS over a 21 month follow-up period when compared with placebo. The apparent beneficial effect of riluzole, however, was primarily in the subgroup of patients with bulbar-onset disease. The effectiveness of riluzole for ALS patients with limb-girdle onset disease remains uncertain.
PERIPHERAL NEUROPATHY

Peripheral neuropathy is a general term for any disorder affecting the peripheral nerves. Since peripheral nerves contain motor, sensory, as well as autonomic fibers, symptoms referable to these three components are seen, including weakness and atrophy of muscles, sensory deficits and autonomic disturbances.

There are many ways to classify peripheral neuropathy. One helpful method considers the distribution of nerve involvement, etiology and pathology.

Symmetrical Generalized Polyneuropathy:

This form of neuropathy produces signs and symptoms in a distal-to-proximal gradient, the so-called "stocking-glove" pattern. The reason for this is that the pathologic process causing the neuropathy affects protein synthesis in the cell body of the peripheral nerve. Hence, neuronal dysfunction will first occur in the distal portions of the longest axons, and thus produce symptoms of weakness and numbness in the most distal portions of the extremities, i.e. the feet and hands.

There are four major etiologies for symmetrical polyneuropathies, namely hereditary, toxic-metabolic, systemic disorders, and immune mechanisms.

Hereditary:

This is a large group of disorders in which the onset of symptoms is insidious and progression is indolent over years or decades. Hereditary sensory-motor neuropathy (HSMN) type I - (Charcot-Marie Tooth disease) is the most common hereditary neuropathy, and has an autosomal dominant pattern of inheritance. Phenotypic expression is often variable, such that affected family members of a propositus may have no symptoms and minimal neurologic findings. Characteristic clinical findings include striking atrophy of the calves, resulting in an inverted "champagne bottle" appearance to the lower extremities. Peripheral nerves are often papably enlarged. Large fiber sensory loss is present, with a marked reduction in vibratory perception and proprioception. Ankle jerk reflexes are lost. This neuropathy is typically demyelinating, and nerve conduction velocity measurements are characteristically slow, at approximately 50% of normal values.

Toxic/metabolic:

Numerous drugs and toxins can cause peripheral neuropathy, and these are listed in Table 2.
TABLE 2
TOXIC AND METABOLIC CAUSES OF NEUROPATHY

<table>
<thead>
<tr>
<th>TOXINS</th>
<th>DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercury</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Lead</td>
<td>Cis-platinum</td>
</tr>
<tr>
<td>Zinc</td>
<td>Dapsone</td>
</tr>
<tr>
<td>Arsenic</td>
<td>INH</td>
</tr>
<tr>
<td>Thallium</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Pyridoxine</td>
</tr>
<tr>
<td>Organophosphates</td>
<td>Vincristine</td>
</tr>
<tr>
<td></td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td></td>
<td>ddi</td>
</tr>
<tr>
<td></td>
<td>ddc</td>
</tr>
</tbody>
</table>

Neuropathy Associated With Systemic Diseases:

Numerous systemic diseases are associated with neuropathy, and these are listed in Table 3. **Diabetes mellitus** is perhaps the most common cause of neuropathy in the United States. Both symmetric and asymmetric diabetic neuropathies can occur, as follows:

a) **Symmetric polyneuropathies** are the most common, and include a sensory motor polyneuropathy and an autonomic neuropathy.

b) **Asymmetric neuropathies** are less common. **Mononeuropathy multiplex** results in simultaneous dysfunction of several peripheral nerves, and is due to ischemic infarction of the vasa nervorum. **Cranial neuropathies, truncal radiculopathies and diabetic amyotrophy** (ischemic infarction of the lumbosacral plexus) are other forms of asymmetric neuropathies. **Entrapment neuropathies**, including carpal tunnel syndrome, are also commonly seen in diabetics.

TABLE 3
SYSTEMIC DISEASES ASSOCIATED WITH NEUROPATHIES

**Systemic Diseases**

- Diabetes mellitus
- Uremia
- Porphyria
- Vitamin B₁₂ deficiency
- Amyloidosis
- Hypothyroidism
- Benign monoclonal gammopathy

**Vasculitides**

- Systemic lupus erythematosus
- Rheumatoid arthritis
- Polyarteritis nodosa
- Cryoglobulinemia

**Systemic Infections**

- Leprosy
- Syphilis
- Diphtheria
- HIV

**Cancer**

- Hodgkin’s disease
- Multiple myeloma
- Oat cell carcinoma
Immune-mediated neuropathies:

In this group of disorders, an immune-mediated attack on peripheral nervous system myelin is the characteristic pathologic change. Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) are the two most common forms in this group.

GBS is a monophasic, immune-mediated demyelinating neuropathy that frequently follows a viral infection and causes an acute and oftentimes severe progression of weakness and numbness over several weeks. CIDP is a chronic demyelinating neuropathy that can have a slowly progressive or a relapsing course. In both of these neuropathies, antibodies have been found that cross-react with peripheral nerve myelin.

The demyelinating neuropathies primarily affect large-diameter, myelinated axons at the start of the illness, and hence produce significant motor weakness and large-fiber sensory loss, including loss of vibratory perception and proprioception. Elevated CSF protein and slowed nerve conduction velocities are the characteristic laboratory findings in this group of neuropathies.

Multifocal neuropathies (mononeuropathy multiplex):

Patients with these forms of neuropathy develop more or less simultaneous dysfunction of several peripheral nerves. The underlying pathologic mechanism is felt to be ischemic infarction of the vasa nervorum due to vasculitis, as can be seen with SLE, rheumatoid arthritis, polyarteritis nodosa, and diabetes mellitus. These neuropathies are frequently painful and cause profound weakness. Prognosis for recovery is good, assuming that the underlying disease process leading to nerve infarction can be suppressed.

Focal neuropathies (mononeuropathies):

Traumatic injuries and entrapment of peripheral nerves at the usual sites of compression are the most common causes of focal mononeuropathy. The most frequently seen entrapment neuropathies are listed in Table 4.

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>NERVE</th>
<th>SITE OF COMPRESSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carpal tunnel syndrome</td>
<td>Median</td>
<td>Wrist</td>
</tr>
<tr>
<td>Tardy ulnar palsy</td>
<td>Ulnar</td>
<td>Elbow</td>
</tr>
<tr>
<td>Saturday night palsy</td>
<td>Radial</td>
<td>Spiral groove in arm</td>
</tr>
<tr>
<td>Peroneal neuropathy</td>
<td>Peroneal</td>
<td>Fibular head</td>
</tr>
<tr>
<td>Tarsal tunnel syndrome</td>
<td>Tibial</td>
<td>Ankle</td>
</tr>
</tbody>
</table>
Summary mnemonic for the etiologies of common neuropathies:

The mnemonic DANG THERAPIST is helpful in recalling the more common causes of peripheral neuropathy, and is listed below:

**DANG THERAPIST**

- Diabetes Mellitus
- Alcohol
- Nutritional (B₁₂ deficiency)
- Guillain-Barré Syndrome
- Toxins (Pb, As, Zn, Hg)
- Hematologic (paraproteins)
- Endocrine (hypothyroid)
- Rheumatologic (SLE, rheumatoid arthritis, vasculitis)
- Amyloid
- Porphyria
- Infectious (syphilis, HIV)
- Sarcoid
- Tumor (paraneoplastic neuropathy)

**NEUROMUSCULAR JUNCTION DISORDERS**

The disorders of neuromuscular junction transmission classically result in fatigable weakness. Myasthenia gravis and the myasthenic syndrome (Eaton-Lambert syndrome) are the two major diseases in this category.

**Myasthenia gravis (MG):**

Myasthenia gravis is an autoimmune disorder caused by antibodies directed against the acetylcholine receptor of skeletal muscle, resulting in weakness and fatigability of voluntary muscles. MG is seen more frequently in women by a ratio of about 3:2. A bimodal distribution of peak incidence is noted, with women having a higher incidence in the third decade and men in the fifth decade.

The symptoms of MG usually begin in one of three groups of muscles: 1) eyes, with ptosis and ophthalomoplegia being cardinal symptoms; 2) bulbar (lower brain stem) musculature, with dysphagia, dysarthria, bifacial and neck weakness being common; and 3) limb and trunk musculature, affecting proximal muscles usually more than distal ones, and frequently involving the respiratory muscles. Pathologic fatigability is a cardinal feature of this disorder, and symptoms of MG are usually more pronounced in the evening.

Numerous factors can cause an exacerbation of symptoms of MG, including systemic infections, thyroid disease, pregnancy, emotional stress, hypokalemia and hypocalcemia.
The thymus gland is abnormal in the majority of patients with MG: 10% have a thymoma, and about 70% have thymic hyperplasia. Thymomas occur more commonly in older patients.

The diagnosis of MG can often be made clinically, looking for pathologic fatigability in voluntary muscles. Since eye signs are common in MG, many patients demonstrate fatigable ptosis with sustained upgaze, which is known as the "curtain sign".

Laboratory confirmation of MG includes the edrophonium (Tensilon) test, electrophysiological studies including repetitive stimulation and single fiber EMG, and serum assay for the acetylcholine receptor antibody. These antibodies are elevated in about 90% of patients with MG and are rarely elevated in other disorders, making this test a very sensitive and specific assay for MG.

Numerous effective treatments are available for MG, and in most cases, the disease can be put into complete remission.

Anticholine esterase medications, including neostigmine and pyridostigmine (Mestinon) are two long acting anticholine esterases that ameliorate the symptoms of MG by inhibiting the breakdown of acetylcholine, permitting it to act longer at the neuromuscular junction. These medications have numerous side effects, including nausea, vomiting, abdominal cramps, diarrhea and fasciculations, which often limit their effectiveness.

Thymectomy is recommended for treating all patients with generalized myasthenia gravis. This procedure is most successful if performed early in the course of the disease, since thymectomy eliminates a potential source of antigenic stimulation for the production of the antibodies associated with MG. Over 90% of patients who undergo thymectomy improve, and many of these achieve a clinical remission. The effects of thymectomy are delayed, however, and are frequently not evident until several years have elapsed.

Immunotherapy including corticosteroids, immunosuppressive drugs, plasma exchange and intravenous immunoglobulin are the mainstays of treatment for MG. These will be discussed below.

Many commonly used drugs have an adverse effect on neuromuscular transmission and should be used with caution in patients with MG. These are listed in Table 6.
TABLE 6
DRUGS WITH ADVERSE AFFECTS AT THE NEUROMUSCULAR JUNCTION

Aminoglycoside antibiotics
- Neomycin
- Streptomycin
- Kanamycin
- Gentamicin
- Tobramycin
- Amikacin

Anti-arrhythmic agents
- Quinidine
- Procainamide
- Propranolol
- Phenytoin
- Calcium channel blockers

Other antibiotics
- Tetracycline
- Bacitracin
- Clindamycin

NMJ blockers
- Succinylcholine
- Curare

Miscellaneous drugs
- Penicillamine

Myasthenic syndrome (Eaton-Lambert syndrome) (ELS):

ELS is a disorder of neuromuscular transmission due to defective acetylcholine release at the presynaptic nerve terminal that results in proximal muscle weakness which improves with repeated effort. This disorder is more common in males by a ratio of 5:1. It is also more frequent in older individuals. The majority of patients with this syndrome, particularly men, have a malignancy of one kind or another, with oat cell carcinoma of the lung being the most common. ELS is also associated with other autoimmune diseases.

In contrast to MG, the extraocular and bulbar muscles are not usually involved in ELS. Muscle stretch reflexes tend to be depressed in this disorder, and peripheral and autonomic nervous system involvement is commonly seen.

Electrodiagnostic studies, including repetitive stimulation, are extremely helpful in making a diagnosis.

Treatment of ELS consists of treating the primary malignancy, if one is present. Corticosteroids, immunosuppressive drugs, as well as plasma exchange have been used successfully in some reports. 3,4-diaminopyridine, an agent that enhances acetylcholine release at the neuromuscular junction, has been found effective in treating ELS in a small number of patients.

Table 7 compares many of the features of ELS with those of MG.
### TABLE 7
NMJ TRANSMISSION DISORDERS

<table>
<thead>
<tr>
<th></th>
<th>MG</th>
<th>ELS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pattern of weakness</td>
<td>Eyes</td>
<td>Proximal limbs</td>
</tr>
<tr>
<td></td>
<td>Bulbar muscles</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Limbs &amp; trunk</td>
<td></td>
</tr>
<tr>
<td>Effect of exercise</td>
<td>Worsens</td>
<td>Improves</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Brisk</td>
<td>Depressed</td>
</tr>
<tr>
<td>PNS &amp; ANS involvement</td>
<td>Absent</td>
<td>Paresthesias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dry mouth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Impotence</td>
</tr>
<tr>
<td>Associated illness</td>
<td>Autoimmune</td>
<td>Autoimmune</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cancer (oat cell)</td>
</tr>
<tr>
<td>M:F ratio</td>
<td>2:3</td>
<td>5:1</td>
</tr>
<tr>
<td>Age distribution</td>
<td>Bimodal</td>
<td>&gt;40 y.o.</td>
</tr>
<tr>
<td>Etiology</td>
<td>AChR antibody</td>
<td>Defect in ACh release</td>
</tr>
<tr>
<td>EMG</td>
<td>Post-exercise decrement</td>
<td>Post-exercise facilitation</td>
</tr>
<tr>
<td>Treatment</td>
<td>Anticholinesterases</td>
<td>3,4-diaminopyridine</td>
</tr>
<tr>
<td></td>
<td>Thymectomy</td>
<td>Treat malignancy</td>
</tr>
<tr>
<td></td>
<td>Steroids</td>
<td>Steroids</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressives</td>
<td>Immunosuppressives</td>
</tr>
<tr>
<td></td>
<td>Plasma exchange</td>
<td>Plasma exchange</td>
</tr>
<tr>
<td></td>
<td>IVlg</td>
<td>IVlg</td>
</tr>
</tbody>
</table>

#### MYOPATHIES

The myopathies are primary disease of muscle, and all produce weakness with variable pain and wasting of skeletal muscle. The myopathies may be divided into three major groups: 1) muscular dystrophies, 2) metabolic myopathies, 3) inflammatory myopathies.

### Muscular dystrophies:

The muscular dystrophies are a group of hereditary myopathies characterized by progressive muscular wasting and weakness. There are five major types of muscular dystrophy: Duchenne, Becker, facioscapulohumeral (FSH), limb girdle, and myotonic muscular dystrophy. The salient features of these muscular dystrophies are summarized in Table 8.
TABLE 8
MUSCULAR DYSTROPHIES

<table>
<thead>
<tr>
<th></th>
<th>Duchenne</th>
<th>Becker</th>
<th>FSH</th>
<th>Limb-Girdle</th>
<th>Myotonic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inheritance</td>
<td>SLR</td>
<td>SLR</td>
<td>AD</td>
<td>AR</td>
<td>AD</td>
</tr>
<tr>
<td>Chromosome</td>
<td>X</td>
<td>X</td>
<td>4</td>
<td>?</td>
<td>19</td>
</tr>
<tr>
<td>Age at onset (yrs)</td>
<td>&lt; 5</td>
<td>&lt; 10</td>
<td>10-20</td>
<td>10-30</td>
<td>15-30</td>
</tr>
<tr>
<td>Initial weakness</td>
<td>Neck</td>
<td>Neck</td>
<td>Shoulder</td>
<td>Pelvic &amp; shoulder</td>
<td>Distal</td>
</tr>
<tr>
<td>Facial involvement</td>
<td>Late</td>
<td>Late</td>
<td>Early</td>
<td>Late</td>
<td>Early</td>
</tr>
<tr>
<td>Rate of progression</td>
<td>Rapid</td>
<td>Slower</td>
<td>Slow</td>
<td>Slow</td>
<td>Slow</td>
</tr>
<tr>
<td>CK</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>Normal</td>
<td>↑</td>
<td>Normal</td>
</tr>
<tr>
<td>ECG</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>Normal</td>
<td>Occ abnl</td>
<td>Abnormal</td>
</tr>
</tbody>
</table>

Duchenne muscular dystrophy:

This is the most rapidly progressive form of muscular dystrophy, and results in progressive muscle weakness and wasting, flexion contractures, ECG changes, respiratory failure and death, usually by the age of 25. The disease has an X-linked recessive pattern of inheritance, although one third of all cases are due to a spontaneous mutation. The abnormal gene responsible for this disorder has recently been sequenced, and the missing protein has been identified as dystrophin, a putative structural protein that may help anchor the contractile elements of skeletal muscle fibers to the cell membrane. The diagnosis of DMD is based on family history, clinical features, and laboratory findings including a markedly elevated serum creatine kinase, myopathic EMG and characteristic muscle biopsy findings.

Becker muscular dystrophy:

This disorder is genotypically and phenotypically related to Duchenne muscular dystrophy but has a much more benign course. Recent investigations suggest that, although the amount of dystrophin in skeletal muscle is normal, the protein is structurally abnormal.

Facioscapulohumeral (FSH) dystrophy:

This muscular dystrophy results in slowly progressive weakness and wasting of facial, scapular, humeral and peroneal muscles. Symptoms generally begin towards the end of the first decade or during the second decade. FSH is slowly progressive and life expectancy is generally not reduced. The disorder has an autosomal dominant form of inheritance, and the abnormal gene has recently been localized to chromosome 4. Diagnosis is based on family history, clinical features and myopathic EMG and muscle biopsy findings.
Limb girdle dystrophy:

This is a heterogeneous group of hereditary muscle disorders, frequently autosomal recessive, which demonstrate slowly progressive hip and shoulder girdle weakness. Onset of symptoms is typically in the second or third decade, and most patients have a slowly progressive clinical course. Cardiac and respiratory complications are common.

Myotonic dystrophy

Myotonic dystrophy is an autosomal dominant disorder characterized by facial and distal muscle wasting and weakness, myotonia (a defect in relaxation of muscle), as well as specific non-muscular manifestations including frontal balding, cataracts, gonadal dysfunction, pulmonary hypoventilation, mild mental retardation and cardiac conduction abnormalities. The abnormal gene responsible for this form of muscular dystrophy is located on chromosome 19. Symptomatic disease onset is generally in the second or third decade, although a severe congenital form of the disease may occur.

The gene lesion in myotonic dystrophy is due to an abnormal expansion of a trinucleotide repeat, CTG, located on the long arm of chromosome 19. Normal individuals have a range of expansion for the trinucleotide CTG repeat that varies between 5 and approximately 30 repeats. Patients with myotonic dystrophy, in contrast, have a CTG trinucleotide expansion that exceeds 50 repeats. An interesting finding is that the number of CTG repeats increases in subsequent generations, and this might be responsible for the increasing severity of findings in successive generations of myotonic dystrophy families, a phenomenon known as anticipation.

The diagnosis of myotonic dystrophy is based on family history, clinical features, and laboratory studies including evidence for electrical myotonia on EMG sampling of muscle, and characteristic muscle biopsy findings.

Metabolic myopathies:

The metabolic myopathies are a heterogeneous group of muscle disorders, in which normal muscle contraction is impaired due to abnormalities in glycoœen or lipid metabolism, endocrine function, electrolyte balance or mitochondria. Table 9 lists the various metabolic myopathies.
### TABLE 9
**METABOLIC MYOPATHIES**

<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
</tr>
</thead>
</table>
| 1. Glycogenoses             | Myophosphorylase deficiency  
|                             | Acid maltase deficiency  
|                             | Phosphofructokinase deficiency  |
| 2. Lipidoses                | Carnitine deficiency  
|                             | Carnitine palmityl transferase deficiency  |
| 3. Endocrine Myopathies     | Hyperthyroidism  
|                             | Hypothyroidism  
|                             | Hyperparathyroidism  
|                             | Corticosteroid myopathy  |
| 4. Periodic Paralyses       | Hyperkalemic  
|                             | Hypokalemic  |
| 5. Mitochondrial Myopathies | Kearns-Sayre syndrome  
|                             | Oculocraniosomatic neuromuscular disease  |

The disorders of glycogen and lipid metabolism characteristically produce symptoms of exercise intolerance. **Acid maltase deficiency**, however, causes a progressive proximal myopathy and respiratory failure, and is clinically similar to the muscular dystrophies. Deficiency of key enzymes in glycogen and lipid metabolism is the cause of these disorders. Most have an autosomal recessive pattern of inheritance. Diagnosis rests on clinical features, particularly exercise intolerance and myoglobinuria following exercise, and laboratory studies including elevations in serum creatine kinase and myopathic features on EMG. Biochemical analysis of muscle biopsy specimens is necessary for exact diagnosis.

Both hypo and hyperthyroidism may produce muscle weakness. Hyperthyroidism typically produces proximal muscle weakness, as well as opthalmoplegia, the latter due to abnormal protein accumulations in extraocular muscles. Hypothyroidism does not cause significant muscle weakness, although many patients may notice muscle fatigue, aching and cramps. **Serum creatine kinase is markedly elevated in many patients with hypothyroidism**, and this may lead to hypothyroid myopathy being misdiagnosed as polymyositis. Thus, serum thyroid levels should be measured in all patients with muscle symptoms and elevated creatine kinase activity. Hypothyroid myopathy responds dramatically to thyroid hormone replacement with rapid and complete resolution of symptoms in most patients.

**Mitochondrial Myopathies:**

The mitochondrial myopathies are a group of disorders with multi-system involvement in which mitochondria have been shown to be morphologically abnormal. Neurological symptoms are common, and five such syndromes have been identified:
1. Kearns-Sayre syndrome (progressive external ophthalmoplegia, retinitis pigmentosa, heart block and elevated CSF protein)
2. Myoclonic epilepsy with ragged red fibers (MERRF)
3. Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS)
4. Pure progressive external ophthalmoplegia
5. Pure skeletal myopathy

Many of these disorders have been found to have abnormalities in mitochondrial DNA, resulting in a pattern of inheritance best described as "maternal", since mitochondria are exclusively inherited from the mother. These defective mitochondrial genomes interfere with the normal function of mitochondria, resulting in a deficiency of ATP generation. It is easy to see how this ATP deficiency may lead to muscle weakness and fatigue, since skeletal muscle, and in particular, extraocular muscles, are metabolically active.

A mitochondrial myopathy should be suspected in any patient with a progressive paralysis of eye movements. The diagnosis is confirmed by finding ragged red fibers in a muscle biopsy specimen, and by means of biochemical analysis of muscle for specific oxidative enzymes.

**Inflammatory myopathies:**

The inflammatory myopathies are a group of acquired muscle diseases in which muscle inflammation produces variable amounts of weakness and pain. Most of these diseases are felt to be autoimmune in origin. There are three major categories of the idiopathic inflammatory myopathies, namely dermatomyositis, polymyositis, and inclusion body myositis. Dermatomyositis is associated with a skin rash, whereas in the latter two disorders inflammation is confined to muscle. Table 10 summarizes the salient features of these three disorders.
TABLE 10
INFLAMMATORY MYOPATHIES

<table>
<thead>
<tr>
<th></th>
<th>Dermatomyositis</th>
<th>Polymyositis</th>
<th>Inclusion Body Myositis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Weakness</td>
<td>Proximal</td>
<td>Proximal</td>
<td>Distal &amp; proximal</td>
</tr>
<tr>
<td>Age at onset</td>
<td>Childhood and &gt; 40</td>
<td>Adults</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>Association with CVD &amp; CA</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sex distribution</td>
<td>M=F</td>
<td>M=F</td>
<td>M&gt;F</td>
</tr>
<tr>
<td>Response to steroids</td>
<td>Good</td>
<td>Variable</td>
<td>Poor</td>
</tr>
<tr>
<td>CK</td>
<td>↑</td>
<td>↑</td>
<td>±</td>
</tr>
<tr>
<td>EMG</td>
<td>Myopathic</td>
<td>Myopathic</td>
<td>Myopathic &amp; neuropathic</td>
</tr>
<tr>
<td>Muscle biopsy</td>
<td>Perifascicular atrophy</td>
<td>&quot;Inflammatory&quot; or NL</td>
<td>Inclusion bodies</td>
</tr>
</tbody>
</table>

**Dermatomyositis:**

Dermatomyositis is a specific inflammatory disorder of muscle that produces a characteristic purple rash over the face, trunk and joints, as well as muscle weakness that is primarily proximal. Non-muscular manifestations are frequently present, and include joint contractures, congestive heart failure, interstitial lung disease, and vasculitis. Children and adults are both affected; a small number of patients have an associated malignancy.

A complement-mediated vasculopathy is felt to be the primary immunologic event causing muscle lesions in dermatomyositis. Immune complexes can be found in the skeletal muscle capillaries, and this results in perivascular inflammation and muscle infarction.

Diagnosis is based on clinical features, elevation in serum CK concentration, a myopathic EMG, and characteristic muscle biopsy findings including muscle fiber necrosis, perivascular inflammation and perivascular atrophy of muscle fibers. Treatment with corticosteroids is extremely effective in many patients, but other patients may require immunosuppressive agents including azathioprine, cyclophosphamide, and methotrexate.

**Polymyositis:**

Polymyositis is a heterogeneous group of inflammatory myopathies that all produce variable degrees of muscle weakness and pain. Unlike dermatomyositis, which has characteristic clinical and pathological findings, polymyositis is much less well defined. Diagnosis is based on clinical findings of muscle weakness and pain, elevated serum CK levels, myopathic EMG findings, and muscle histology demonstrating muscle fiber...
necrosis and inflammatory infiltrates. Treatment is identical to that noted for dermatomyositis, although the response to steroids is variable and incomplete.

**Inclusion Body Myositis:**

Inclusion body myositis is a distinct, slowly progressive inflammatory myopathy of older adults. Both proximal and distal muscles are affected, and prominent atrophy of the flexor compartments of the forearms is an early finding; muscle pain is unusual. Diagnosis is based on characteristic clinical features and muscle biopsy findings demonstrating rimmed inclusion vacuoles and inflammatory cell infiltrates. Serum CK levels are typically normal or only slightly elevated, and EMG findings are non-specific with myopathic and neuropathic features. No proven treatment exists. Although corticosteroids have demonstrated a modest transient improvement in some studies, a sustained response was not seen.

**CRITICAL ILLNESS WEAKNESS**

A small number of critically ill patients with multi-system failure who are treated in an intensive care unit develop severely disabling weakness, oftentimes associated with respiratory failure. Many of these patients are receiving corticosteroids, aminoglycoside antibiotics and neuromuscular junction blocking agents for treatment of their various medical conditions. Four neurological syndromes have been identified as contributing to their muscle weakness:

1. Critical illness polyneuropathy
2. Vecuronium-induced prolonged neuromuscular blockade
3. Focal myosin deficient myopathy
4. Diffuse myosin deficient myopathy

Vecuronium-induced prolonged neuromuscular blockade improves rapidly once the neuromuscular blocking agent is stopped. Recovery for critical illness polyneuropathy or from focal or diffuse myosin deficient myopathy may take weeks to months. The exact cause of these latter three conditions is not known, but is felt to represent an interplay of sepsis, malnutrition, muscle catabolism and disuse.

**EVALUATION OF THE WEAK PATIENT**

The evaluation of a patient with weakness of neurologic origin is relatively straightforward. The first step in this evaluation process is to localize the level of the lesion within the neuraxis: upper motor neuron, anterior horn cell, peripheral nerve, neuromuscular junction, and muscle itself. Findings on history and physical examination are most important in identifying the correct level of the lesion. Laboratory studies, including serum creatine kinase determination, serum antibodies, and results of nerve conduction studies and EMG's help refine the diagnosis. Finally, muscle and nerve biopsy findings will allow one to make a specific diagnosis in the majority of cases.
Table 11 summarizes the clinical and laboratory findings seen in the various neuromuscular disorders.

| TABLE 11 |
|------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| CLINICAL AND LABORATORY FEATURES OF NEUROMUSCULAR DISORDERS | UMN | AHC | PNS | NMJ | MUSCLE |
| Muscle bulk | Preserved | Atrophy | Atrophy | Normal | Normal early on |
| Muscle tone | Spastic | Flaccid | Flaccid | Normal | Normal |
| Weakness | Proximal>distal | Diffuse | Distal | Proximal | Proximal |
| Spontaneous movements | None | Fasciculations | Fasciculations | None | None |
| Reflexes | ↑ | ↓ | ↓ | Normal to ↑ | Normal early on |
| Babinski sign | Present | Absent | Absent | Absent | Absent |
| Sensory sx | Present | None | None | None | None |
| CK | Normal | ↑ | Normal | Normal | ↑↑ |
| EMG | Normal | Neuropathic | Neuropathic | RSS abnormal | Myopathic |
| Muscle bx | Type 2 atrophy | Atrophy | Atrophy | Normal | Necrosis |

HISTORY AND PHYSICAL EXAMINATION

The history and physical examination findings are key in making a proper diagnosis in patients with neurological weakness. Important aspects of the history include the tempo of illness, distribution of weakness, presence or absence of sensory or autonomic symptoms, and involvement of cranial nerve musculature. The family history is crucial, since many neuromuscular disorders are hereditary. Physical examination findings of importance include muscle strength testing, muscle tone, the sensory examination and muscle stretch reflexes.

Anterior horn cell disorders typically produce diffuse weakness, muscle atrophy, hypotonia, fasciculations, and absent muscle stretch reflexes. The sensory examination is typically normal. Patients with amyotrophic lateral sclerosis have, in addition, upper motor neuron findings including hyperreflexia and Babinski signs.

Patients with peripheral neuropathy typically have a combination of motor and sensory findings on examination. The pattern of weakness is typically distal in the symmetrical axonal polyneuropathies, and diffuse in demyelinating polyneuropathies. Muscle tone is decreased and muscle stretch reflexes are absent. Sensory findings are variable: patients with symmetrical, primarily axonal polyneuropathies have loss of small-fiber modalities including pain and temperature perception in a stocking-glove distribution; patients with primarily demyelinating neuropathies have loss of large-fiber sensory modalities including vibratory perception and position sense.

Neuromuscular junction disorders, including myasthenia gravis, result in fatigable weakness that preferentially involves proximal muscle groups and eye and bulbar
musculature, including muscles involved with swallowing and speaking. The sensory examination is normal, and muscle stretch reflexes are frequently normal as well.

Patients with myopathic disorders initially develop symmetrical, proximal muscle weakness. Muscles may be tender to palpation, particularly with the inflammatory myopathies. Atrophy of muscle is a late finding in these disorders, and muscle stretch reflexes are typically normal early in the course of these diseases. The sensory examination is invariably normal.

LABORATORY

Creatine kinase: Creatine kinase (CK) is an enzyme that is primarily found in brain and muscle, both skeletal and cardiac. Different isoenzymes occur, and the MM fraction is the isoenzyme that is primarily found in skeletal muscle. Serum CK activity is increased significantly in most of the inflammatory myopathies including polymyositis and dermatomyositis. CK elevations are also found in most of the active myopathies including Duchenne, Becker, and limb-girdle muscular dystrophy, glycogen and lipid storage diseases of muscle, and hypothyroid myopathy. Serum CK activity may be slightly increased (2-3 times normal) in anterior horn cell diseases and severe axonal neuropathies with significant denervation. Creatine kinase levels are normal in patients with demyelinating neuropathies, as well as in all of the neuromuscular junction disorders.

Autoantibodies are present in many of the immune-mediated neuromuscular diseases. The acetylcholine receptor antibody is present in approximately 90% of patients with myasthenia gravis. The antistriatal muscle antibody is present in the majority of patients with myasthenia gravis who have a thymoma. Anti Jo antibodies are present in many patients with polymyositis and dermatomyositis. The anti Hu antibody is found in some paraneoplastic neuropathies, particularly those associated with oat cell carcinoma of the lung. Anti-GM-1 antibodies may be found in patients with multifocal neuropathies with conduction block.

NERVE CONDUCTION STUDIES AND ELECTROMYOGRAPHY

Nerve conduction study:

A nerve conduction study is the recording and measurement of the compound nerve and muscle action potentials that are elicited in response to a single supramaximal electrical stimulus. The terminal latency, amplitude, and duration of the evoked potential are recorded, as well as the conduction velocity.

Nerve conduction studies are helpful in documenting that a neuropathy exists, quantitating the severity, and noting the distribution of the neuropathy, i.e. whether it is distal, proximal or diffuse. In addition, nerve conduction studies can provide information on the modality involved, i.e. motor versus sensory, and can also give clues as to the underlying pathology, whether axonal or demyelinating.
Demyelinating neuropathies (neuropathies due to loss or destruction of myelin) result in slowed conduction velocities and prolonged distal latencies, because conduction velocity is proportional to the velocity of the largest-diameter myelinated fibers.

Axonal neuropathies (neuropathies due to loss of axons or their cell bodies) generally result in a reduced amplitude of the compound motor or sensory nerve action potentials.

**Electromyography (EMG):**

EMG is the recording and study of insertion, spontaneous, and voluntary electrical activity of muscle. This test allows one to physiologically evaluate the motor unit, including the anterior horn cell, peripheral nerve, and muscle. EMG is helpful when evaluating patients with weakness, in that it can help one to determine whether the weakness is due to anterior horn cell disease, nerve root compression, peripheral neuropathy, or an intrinsic disease of muscle itself (myopathy).

EMG can differentiate active (inflammatory) myopathies from chronic myopathies, and may thus help one to better characterize the pathologic process involved. In active myopathies, fibrillations and positive waves are present in the muscle fiber at rest. In chronic myopathies, the voluntary motor unit potentials are of low amplitude and short duration and are frequently polyphasic. Recruitment may be rapid.

EMG can also differentiate acute denervation from chronic denervation, and may thus give an indication as to the time course of a neuropathy. In acute denervation, fibrillations and positive waves are present, indicating spontaneous discharge of individual muscle fibers. In chronic denervation, the voluntary motor unit potentials are of large amplitude and long duration and are frequently polyphasic, because the motor units are enlarged as a result of re-innervation of adjacent previously denervated muscle fibers. Recruitment of additional motor units in response to increasing the force of muscular contraction is reduced for the same reason.

**MUSCLE AND NERVE BIOPSIES**

**Muscle Biopsy:**

Skeletal muscle is frequently examined by a biopsy in two settings: 1) a generalized disease with multi-organ involvement (e.g. sarcoidosis or vasculitis) in which one desires to have a safe and easy source of tissue; and 2) a primary neuromuscular disease in which pathology is confined to muscle. It is important to note that in both of these settings, muscle pathology is frequently multifocal and not diffuse. Hence, if an uninvolved area of muscle is inadvertently biopsied, one may get false negative results due to sampling error. In such situations, repeat biopsy may be necessary.

Muscle biopsies should be performed in specialized centers that have a laboratory which can process and stain frozen muscle specimens using a full battery of histologic stains and histochemical reactions, including the modified Gomori trichrome stain, NADH, ATPase, PAS, oil red O, and acid phosphatase. Frozen preparation of muscle is necessary, since formalin fixation destroys muscle fiber architecture and inactivates many of the enzymes that are helpful in making an accurate diagnosis. Electron
**Microscopy** of muscle specimens is helpful to study the ultrastructure of muscle fibers, including mitochondria, lysosomes, glycogen granules, lipid accumulation and virus particles. **Biochemical analysis** of muscle is helpful in identifying specific enzyme deficiencies and glycogen or lipid storage diseases.

Various pathologic changes can occur in skeletal muscle, including changes in fiber size and shape, abnormalities in the distribution of fiber types, changes in the sarcolemmal nuclei, degeneration and regeneration of muscle fibers, and inflammatory infiltrates. By noting the presence of these pathologic changes, one can usually decide if a primary myopathic or neuropathic process is occurring. At times, specific pathologic changes may be found that point to a particular diagnosis.

**Nerve biopsy:**

There are few indications for nerve biopsy when evaluating peripheral neuropathy. In general, a nerve biopsy is performed to evaluate asymmetric, multi-focal neuropathies. The *sural nerve* is frequently biopsied, since this is a purely sensory nerve that is easily obtained. In the upper extremity, the superficial radial nerve may be biopsied if necessary.

The nerve specimen is typically evaluated by means of light and electron microscopy. Semi-thin plastic embedded sections, stained with toluidine blue, are helpful for evaluating the myelin sheaths. Teased nerve fiber preparations are also helpful to look for demyelination and remyelination.

Sural nerve biopsies are particularly helpful when evaluating patients with a clinical picture of mononeuropathy multiplex, the basis of which is still unclear after other laboratory investigations are complete. Vasculitis, amyloidosis, leprosy and sarcoidosis can be accurately diagnosed by means of nerve biopsy.

Performing a nerve biopsy routinely in the evaluation of symmetric, cistal polyneuropathies is usually fruitless, in that the pathologic diagnosis most often reveals "chronic neuropathy with mixed axonal-demyelinating features", a non-specific finding of little clinical importance.

**TREATMENT OF NEUROMUSCULAR DISEASES**

**Immune-Mediated Therapies**

The immune-mediated therapies include corticosteroids, immunosuppressive agents, plasmapheresis and intravenous immunoglobulin (IVIg). These treatments are quite effective in treating the immune-mediated neuropathies and myopathies.

**Corticosteroids:**

By virtue of their immunosuppressive effects, corticosteroids have been found to be effective in treating the vasculitic neuropathies (those associated with SLE, rheumatoid arthritis or polyarteritis nodosa), chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, as well as the inflammatory myopathies, including dermatomyositis.
and polymyositis. Recent clinical studies suggest that corticosteroids may improve function in patients with Duchenne muscular dystrophy, but the results of long-term trials are needed before this treatment can be recommended for all Duchenne patients.

Corticosteroids may be given daily or on an every-other-day regimen, depending on the severity and tempo of the disease. The typical initial dose of corticosteroids for the treatment of inflammatory neuromuscular disorders is 1 mg/kg/day of prednisone (or 2 mg/kg every other day).

Corticosteroids have never been proven to be effective in treating Guillain-Barré syndrome, and hence are not recommended for this disorder.

**Immunosuppressives:**

Azathioprine, cyclophosphamide, cyclosporine and methotrexate are all used in the treatment of autoimmune neuromuscular diseases. Each of these medications has potential serious toxicity.

**Azathioprine** is frequently used, in combination with steroids, to treat autoimmune neuropathies, myopathies and myasthenia gravis, because of its steroid-sparing effects. Concurrent use of these two medications allows corticosteroids to be tapered more quickly and more completely once the disease is brought under control.

The usual dosage of azathioprine is 2-3 mg/kg per day given in divided doses. This medication has a delayed beneficial effect and several months are required before an effect may be seen. The erythrocyte mean cell volume (MCV) provides an index of therapeutic effect: a slight elevation in MCV suggests that the dose of azathioprine is appropriate.

Azathioprine is metabolized by xanthine oxidase and medications that block this enzyme, such as allopurinol, should be avoided since concurrent use can cause azathioprine toxicity.

**Plasma exchange:**

In this procedure, blood is removed from the patient, plasma is separated from blood cells and discarded, and blood cells are resuspended in colloid solution and reinfused. Plasma exchange is effective in treating patients with immune-mediated neuropathies, such as those caused by cryoglobulins, SLE, rheumatoid arthritis or polyarteritis nodosa. In addition, individuals with GBS and a large subset of patients with CIDP benefit from this procedure.

Plasmapheresis should be considered in any patient with severe signs of myasthenia gravis, and is usually performed when initiating corticosteroids. When performed in this setting, significant clinical improvement may be seen within two weeks of initiating this procedure. In addition, a short course of plasmapheresis is helpful when preparing a patient for thymectomy.

The effects of plasma exchange can be summarized as "fast, temporary and expensive". This procedure does not, by itself, induce permanent remission, and the ideal application is therefore in acute, self-limited disorders such as GBS. Plasma exchange may also
have application in chronic diseases, such as CIDP and MG, where rapid therapeutic
effects may occasionally be required.

**Intravenous immunoglobulin (IVlg):**

IVlg is pooled human IgG in a form that is safe for intravenous administration. How IVlg
affects immunologic function is unknown, but three putative mechanisms have been
postulated:

- Administration of IVlg floods the recipient with an enormously diverse array of
  antibody molecules, some of which are anti-idiotypic antibodies that may neutralize
  autoantibodies in the patient, thereby increasing their clearance and perhaps down
  regulating their production.
- IVlg inhibits the binding of activated complement to target cells, thus reducing
  complement-mediated damage to cell membranes.
- IVlg infusion is a potent stimulus that down regulates immunologic production.

To date, IVlg has been found to be as effective as plasma exchange in treating many
immunologic disorders, including Guillain-Barré syndrome, CIDP, and myasthenia
gravis. IVlg is also reported to be beneficial in treating the polyneuropathy associated
with IgG or IgM paraproteins.

Side effects of IVlg include fever, myalgia, headache, rash and occasionally aseptic
meningitis and renal failure. The cost of IVlg is equivalent to that of plasma exchange.

**PAIN MANAGEMENT**

Numerous symptomatic treatments for the pain of peripheral neuropathy are available,
and all have their relative risks and benefits.

**Tricyclic Compounds:**

The tricyclic anti-depressants, including amitriptyline, desipramine and nortriptyline, are
all of some benefit in treating the painful peripheral neuropathies. Their mechanism of
action is unknown, but is felt to be due to their ability to block the reuptake of
catecholamines. Dosages much lower than those used to treat depression are
frequently adequate for pain control. Since many patients with painful peripheral
neuropathy have worsening of their symptoms at bedtime, amitriptyline and nortriptyline
may be particularly effective in this group of patients because of their sedative effects.

The selective serotonin reuptake inhibitors (SSRI), including fluoxetine, may also be of
benefit in treating the pain of peripheral neuropathy, although evidence is less
convincing.

**Anticonvulsants:**

Gabapentin, one of the new anticonvulsants, has been found to be particularly effective
in treating painful diabetic peripheral neuropathy. Although most patients tolerate it quite
well, it is sedating at high doses.
Phenytoin and carbamazepine are also helpful in treating painful peripheral 
neuropathies. The dosages employed are similar to those used for treating epilepsy. 
Both of these medications cause ataxia, and this may limit their clinical usefulness in 
treating neuropathy. Carbamazepine has been found particularly helpful in treating the 
pain associated with trigeminal neuralgia.

**Topicals:**

Capsaicin, a drug that impedes pain transmission by depleting substance P from 
sensory nerve fibers, has been found effective in treating refractory neuralgia in several 
studies. The cream must be applied several times daily to be effective, and patients 
frequently experience severe burning following each application for one or two weeks 
following initiation of treatment.

**PHYSICAL THERAPY**

Physical therapy is crucial in preventing joint contractures, and in maintaining and 
improving strength in practically all patients with neuromuscular diseases. Physical 
therapy is especially important in patients with slowly progressive hereditary 
neuropathies and myopathies, including Duchenne and Becker muscular dystrophy. 
Performing range of motion exercises in acute neuromuscular disorders, such as 
Guillain-Barré syndrome and myasthenia gravis, is of crucial importance in preventing 
the development of joint contractures in these diseases.
Annotated Bibliography


   In a prospective, double-blind, placebo-controlled trial in 155 outpatients with ALS, 74% of patients taking riluzole were alive at 12 months, as compared with 58% of the placebo group. The difference in survival was even greater in patients with bulbar-onset disease. Adverse reactions to riluzole included asthenia, spasticity and mild elevations in AST levels.


   A succinct review of the various neuropathies associated with MGUS, Waldenstrom's macroglobulinemia, multiple myeloma, POEMS syndrome, and primary systemic amyloidosis. An algorithm for evaluating neuropathies associated with plasma cell dyscrasias is included, as well as a flow chart for evaluating neuropathy associated with MGUS.


   An in-depth review of the three most common acquired inflammatory myopathies. The clinical manifestations, diagnostic studies, and immune and viral pathomechanisms are described in detail. Effective treatment strategies are outlined, including the use of corticosteroids and other immunosuppressive agents.


   An excellent review of this emerging group of disorders. The various defects involving both mitochondrial and nuclear DNA in these diseases are discussed in detail. A helpful flow chart summarizes the diverse clinical features, inheritance patterns, laboratory studies, brain imaging, muscle biopsy findings, muscle biochemistry, and molecular genetics of these disorders.


   An excellent, "up-to-date" summary of the clinical features, immunopathogenesis, diagnosis, and treatment of this disorder. The role of anticholinesterase agents, thymectomy, corticosteroids, other immunosuppressives, plasma exchange and IVlg are all discussed in detail.


   An excellent update on this major idiopathic inflammatory myopathy. A helpful table lists the specific diagnostic criteria for this disorder. The role of amyloid proteins, immune considerations, myonuclear alterations, and mitochondrial abnormalities are all reviewed in detail. Prednisone and IVlg have been studied in several small trials, but results have been inconclusive.

In a randomized, placebo-controlled study in 99 boys with DMD, prednisone at a dose of 0.75 mg/kg/d was beneficial in increasing muscle mass by 36%, and this effect was maintained for 18 months. Side effects of prednisone were common and included weight gain and growth retardation. Azathioprine did not have a beneficial effect.


The authors describe their experience treating 19 patients with LEMS with 3,4-DAP over a 10-year period. Adding pyridostigmine to the treatment regimen may potentiate the effects of 3,4-DAP. Response to treatment may be effectively monitored by means of routine electrophysiological repetitive nerve stimulation studies.


In two randomized, double-blind, crossover trials in 84 patients with painful diabetic peripheral neuropathy, moderate or greater pain relief was seen in 74% of patients receiving amitriptyline, 61% receiving desipramine, 48% receiving fluoxetine, and 41% receiving placebo. Amitriptyline and desipramine were equally effective in both depressed and non-depressed patients, but fluoxetine was effective only in depressed patients.


An excellent review of the Guillain-Barré syndrome, including its clinical features, outcome, rehabilitation, immunopathological mechanisms, and treatment. The use of plasma exchange and intravenous immunoglobulins is discussed in detail.


In a prospective analysis of 21 patients with prolonged ventilator dependency, none of whom had prior neuromuscular disease, 62% were found to have a neuromuscular disease severe enough to account for ventilator dependency. Most of the remaining cases had a contributory neuromuscular disease. Critical illness polyneuropathy was the most common disorder seen, but myopathies, mononeuropathy multiplex, unsuspected porphyria and motor neuron disease were also identified.


An excellent overview comparing the physiology, mechanisms of action and clinical usefulness of PEx and IVlg. A helpful table is provided that lists the diseases for which these treatments have proven effective, those in which they may be effective, and the potential complications, limitations and costs of these two treatments.
HISTOPATHOLOGY OF SKELETAL MUSCLE

Ralph F. Józefowicz, MD

HISTOLOGY OF NORMAL MUSCLE

Muscle Structure

Human skeletal muscle is made up of numerous longitudinally oriented muscle fibers. Muscle fibers, in turn, are made up of hundreds of myofibrils each separated from other fibrils by the intermyofibrillar space. Myofibrils, in turn, are made up of myofilaments. These myofilaments consist of thin actin and thick myosin filaments. The thick myosin filaments are arranged in a parallel fashion and extend throughout the length of the dark, anisotropic or A band. Interdigitating with the thick filaments of myosin are the thin filaments of actin that make up part of the light, isotropic or I band.
The intermyofibrillar space contains mitochondria, glycogen granules and lipid. The sarcoplasmic reticulum and the transverse tubular "T" system weave through and surround the myofibrils. Muscle nuclei in normal, adult muscle usually lie beneath the muscle cell membrane, the sarcolemma. During cell regeneration, these nuclei move centrally.

Within muscle are a number of other structures, including tendon, blood vessels, intramuscular nerves, muscle spindles, connective tissue and adipose tissue.

Muscle Fiber Types

In man, muscle fibers can be divided into two major categories, based on their anatomic appearance, twitch speed, resistance to fatigue, and presence of glycolytic or oxidative enzymes.

**Type 1 muscle fibers** are primarily used to maintain posture, and hence have a high resistance to fatigue and a slow twitch speed. They are dark in appearance due to a high capillary density, and they rely on oxidative metabolism, and hence contain a large number of mitochondria.

**Type 2 muscle fibers** are activated when quick bursts of energy are needed. They have a low resistance to fatigue and a fast twitch speed. They have fewer capillaries and are therefore light in appearance. Their main energy supply is anaerobic glycolysis. Type 2 muscle fibers can be further subdivided into **Type 2A and Type 2B muscle fibers** based on specific histochemical, biochemical and contractile properties, but this sub-classification of Type 2 fibers is not generally useful in the study of muscle pathology.

The following table lists the salient features of Type 1 and Type 2 muscle fibers:

<table>
<thead>
<tr>
<th></th>
<th>Type 1 fibers</th>
<th>Type 2 fibers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomic appearance</td>
<td>Red (dark)</td>
<td>White (light)</td>
</tr>
<tr>
<td>Twitch speed</td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td>Resistance to fatigue</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Glycolytic enzymes</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Oxidative enzymes</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>

**Enzymatic Stains**

- NADH: +    -
- SDH: +     -
- Phosphorylase: - +
- ATPase (Ph 9.4): - +

Type 1 and Type 2 muscle fibers can be differentiated histologically by means of certain enzymatic stains. The ATPase reaction is the most useful in this regard. With preincubation at pH 9.4 (routine ATPase stain), Type 1 muscle fibers are light in appearance and Type 2 muscle fibers are dark. By varying the pH of the ATPase histochemical reaction, Type 2 muscle fibers can be further subclassified into Type 2A and 2B.
Some authors also identify another class of Type 2 fibers, Type 2C fibers, based on these histochemical reactions. Type 2C fibers are felt to be undifferentiated or precursor fibers that are rare in normal human muscle, but increased in number in regenerating muscle. Other enzymatic stains, including NADH, succinic dehydrogenase (SDH), phosphorylase and PAS can also differentiate muscle fiber types, but these reactions are less specific than the ATPase reaction.

<table>
<thead>
<tr>
<th>Muscle fibre type</th>
<th>1</th>
<th>2A</th>
<th>2B</th>
<th>2C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine ATPase (pH 9.4)</td>
<td>●</td>
<td>●</td>
<td>●</td>
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</tr>
<tr>
<td>ATPase pre-incubated pH 4.6</td>
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<td>●</td>
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</tr>
<tr>
<td>ATPase pre-incubated pH 4.3</td>
<td>●</td>
<td>●</td>
<td>●</td>
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</tr>
<tr>
<td>NADH-TR</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>SDH</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Menadione-linked α-glycerophosphate</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>PAS</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Phosphorylase</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

○ = 0  ● = 1+  ● = 2+  ● = 3+

**The Motor Unit**

The motor unit is the final common pathway for motor activity in the nervous system, and muscle is the final effector of the motor unit. The motor unit is composed of the anterior horn cell, its peripheral axon, the axon's terminal branches, the associated neuromuscular junctions, and the muscle fibers that they innervate. The number of muscle fibers per motor unit vary from as few as 10 in the extraocular muscles, to nearly 2000 in leg muscles such as the gastrocnemius.
All muscle fibers within the same motor unit are of identical histochemical type. Convincing experimental evidence indicates that the firing pattern of the anterior horn cell determines the muscle fiber histochemical type. Cross-innervation experiments in animals have shown that muscle fibers will change their histochemical types in response to changing their innervation. If nerve fibers innervating a muscle that is totally composed of Type 1 fibers are implanted into a muscle that normally is composed exclusively of Type 2 fibers, the Type 1 nerve fibers will convert the previously staining Type 2 muscle fibers into Type 1 muscle fibers. Although the exact means by which the individual nerve fibers determine muscle fiber type is not totally clear, the pattern of firing of the neuron is felt to be a major controlling factor.

In lower animals, individual muscles are totally composed of one fiber type. In the chicken, for example, the breast muscle, which is used rather infrequently to beat the chicken's wings, is composed almost entirely of Type 2 muscle fibers (white meat). The leg muscles, on the other hand, are used continuously to maintain posture and are composed almost entirely of Type 1 muscle fibers (dark meat). In man, the situation is quite different. Human muscles contain a more or less equal mixture of Type 1 and Type 2 muscle fibers within the muscle belly. Furthermore, the muscle fibers of each motor unit are not grouped together within the muscle belly, but rather are intermingled with muscle fibers belonging to other motor units, creating a mosaic or checkerboard pattern when visualized with enzymatic stains, such as the ATPase stain, that distinguish muscle fiber types. Loss of this normal checkerboard appearance of muscle can occur with long-standing denervation, with an opportunity for nerve to regenerate. Groups of muscle fibers of the same histochemical type will occur (so-called type grouping), because reinnervation occurs from surviving adjacent nerve fiber collaterals of a single axon.

**PRINCIPLES OF MUSCLE BIOPSY**

Human skeletal muscle is frequently examined by biopsy in two settings:

- A generalized disease with multi-organ involvement (e.g. sarcoidosis or vasculitis) in which one desires to have a safe, easy source of tissue.

- A primary neuromuscular disease in which pathology is confined to muscle.

It is important to note that in both of these settings, muscle pathology is frequently multifocal and not diffuse. Hence, if an uninvolved area of muscle is inadvertently biopsied, one may get false negative results due to sampling error. In such situations, repeat biopsy may be necessary.

**Muscle Biopsy Procedure**

**Selection of Muscle for Biopsy**

Muscles which are technically easy to biopsy, and for which normal data exist are most suitable. These include the biceps, deltoid, quadriceps femoris and gastrocnemius muscles. Muscles that should not be biopsied include:
• Ones subject to trauma, such as EMG, IM injections, accidents or surgery.

• Concomitant denervation, such as the gastrocnemius in older patients due to the high incidence of lumbar nerve root compression in this population.

• Antecedent illness, such as muscles affected by polio years earlier.

In patients with acute neuromuscular illnesses, the weakest muscle should be biopsied, since this muscle may manifest the most pathology. In patients with chronic diseases, the least affected muscle should be biopsied, since more severely affected muscles typically show advanced, nonspecific changes (end stage muscle).

**Technique of Muscle Biopsy**

• **Needle Biopsy** - This is a quick and easy procedure in which multiple areas can be sampled from the same incision. A minimal scar results (5-10 mm).

• **Open Biopsy** - This is a longer procedure that results in a larger scar, but by which a larger sample of muscle can be obtained.

**Fixation Technique**

**Frozen Preparation**

Muscle is best processed frozen, since freezing best preserves muscle architecture and allows enzymatic staining to be performed on the frozen tissue. The muscle tissue is oriented prior to freezing, such that all of the fibers are perpendicular in the section.

**Formalin Fixation**

This method is excellent for blood vessels and nerves, but poor for muscle fiber architecture. Formalin destroys muscle fiber architecture, unlike its effects on most other tissues in which definition is improved.

**Electron Microscopy**

This method allows the study of ultrastructure of muscle fibers, including mitochondria, lysosomes, glycogen granules, lipid accumulation and virus particles. Most changes, however, are non-specific, and of little usefulness in diagnosis.

**Biochemistry**

Muscle can be assayed for specific enzymes, lipids, carbohydrates and proteins, and hence storage or deficiency diseases of muscle can be identified.
**Histological and Histochemical Stains and Reactions**

**Histologic Stains**

These are most useful for evaluating muscle fiber morphology, nuclei, cellular reactions and some architectural changes. The two histological stains that are routinely used in muscle pathology are the modified Gomori trichrome, and the hematoxylin and eosin (H&E) stains.

**Histochemical Reactions**

These stains demonstrate specific enzymatic, glycogen and lipid content of skeletal muscle. Several are routinely employed:

- **NADH** - This is an oxidative enzyme, and hence can differentiate fiber types, with Type 1 fibers staining darkly, and Type 2 light. The stain is also useful for evaluating the intermyofibrillar network, as well as for identifying target fibers and angular fibers, which can be seen in denervation.

- **Succinic Dehydrogenase (SDH)** - This oxidative enzyme has a particular affinity for mitochondria. It is most useful in demonstrating "ragged red fibers", which are subsarcolemmal collections of mitochondria that are present in the mitochondrial myopathies.

- **ATPase** - This enzyme is most useful for differentiating fiber types. Depending on the pH of pre-incubation, the various fiber types stain darkly, as indicated in the following figure. At pH 9.4 (routine), Type 1 fibers stain light and Type 2 dark. Acid (pH 4.2) pre-incubation reverses fiber typing.

---

**Table 3.2**. A diagrammatic representation of the pH sensitivity of the ATPase reaction in human muscle fibre types. Following five minutes preincubation at the values indicated, the various fibre types stain darkly, as indicated by the bars. The shading at the end of each bar indicates that there is a progressive loss of stain as the critical pH is approached. This pH range is also dependent upon the time of incubation.

<table>
<thead>
<tr>
<th>MUSCLE FIBER TYPE</th>
<th>3.5</th>
<th>4.0</th>
<th>4.5</th>
<th>5.0</th>
<th>9.0</th>
<th>9.5</th>
<th>10.0</th>
<th>10.5</th>
<th>11.0</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
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<tr>
<td>2A</td>
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<td>2B</td>
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<td></td>
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<tr>
<td>2C</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
• **Periodic Acid Schiff (PAS)** - This stain demonstrates *glycogen deposits*, and hence is most helpful in screening patients for glycogen storage diseases.

• **Oil Red O** - This is a *lipid stain*, and hence is useful in screening patients for disorders of lipid metabolism, such as carnitine deficiency.

• **Acid Phosphatase** - This enzyme is localized mainly in lysosomes and may thus be used to indicate foci of degeneration and necrosis within muscle fibers.

• **Phosphorylase** - This is a glycolytic enzyme, which is deficient in Type V glycogenosis (McArdle's disease).

• **Myoadenylate Deaminase** - This enzyme is deficient in certain disorders of purine nucleotide metabolism.

**Histology of Normal Muscle**

Normal human skeletal muscle is characterized by relative uniformity of size and shape of muscle fibers as noted in the following table. Muscle fibers in adult males have a slightly larger diameter, due to the anabolic effects of testosterone on Type 2 muscle fibers. Normal human muscle fibers are typically polygonal in shape.

<table>
<thead>
<tr>
<th>Fiber size</th>
<th>Male 40-80μ, female 30-70μ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiber shape</td>
<td>Polygonal</td>
</tr>
<tr>
<td>Fiber distribution</td>
<td>Mosaic checkerboard</td>
</tr>
<tr>
<td>Ratio of Type 1 to Type 2</td>
<td>1:2</td>
</tr>
<tr>
<td>Sarcolemmal nuclei</td>
<td>&lt; 3% internal</td>
</tr>
<tr>
<td>Endomysial connective tissue</td>
<td>Minimal</td>
</tr>
</tbody>
</table>

There are twice as many Type 2 muscle fibers as there are Type 1 muscle fibers in normal muscle, and these are randomly distributed in a checkerboard pattern. Most muscle fiber nuclei are at the periphery, except in regenerating muscle fibers. Internal nuclei should be present in fewer than 3% of all muscle fibers. Endomysial connective tissue is normally only minimally present.

**Pathologic Changes Seen in Muscle Biopsies**

Various pathologic changes can occur in skeletal muscle, including changes in fiber size and shape, abnormalities in the distribution of fiber types, changes in sarcolemmal nuclei, degeneration and regeneration, cellular reactions, as well as specific architectural changes. By noting the presence of these pathologic changes, one can usually decide if a primarily myopathic or neuropathic process is occurring. At times, specific pathologic changes may be found that point to a specific diagnosis.
Myopathic Changes

Pathologic changes suggestive of a myopathy include rounding of muscle fibers, hypertrophy of fibers, and an increase in internal nuclei.

- In chronic myopathies, endomysial connective tissue is increased, and one may see fiber splitting as well as ring fibers.

- In acute myopathies, prominent necrosis and phagocytosis of muscle fibers are present, as well as basophilic fibers, indicating regenerating muscle.

- Inflammatory myopathies are characterized by the presence of inflammatory cell infiltrates.

- Other myopathic changes include Type 1 fiber predominance, as well as moth-eaten and whorled fibers, which are characteristically seen on the NADH stain.

Neuropathic Changes

Pathologic changes suggestive of a neuropathy are often divided into those consistent with recent denervation, as well as those consistent with chronic denervation.

- Changes suggestive of recent denervation include small, angular (shrunken) fibers, as well as pyknotic nuclear clumps, which are clumps of nuclei that remain after the muscle cell cytoplasm has atrophied completely.

- Changes suggestive of chronic denervation include target fibers, fiber type grouping and grouped atrophy. In fiber type grouping, the muscle loses the normal checkerboard appearance, and large groups of Type 1 and Type 2 muscle fibers are seen. This is due to reinnervation of denervated muscle fibers by adjacent axon collateral sprouts, which will all belong to a single motor unit, and hence will be of the same muscle fiber type. In grouped atrophy, large groups of atrophic fibers, all belonging to the same muscle fiber type, are seen. This occurs when reinnervated muscle fibers belonging to a large motor unit subsequently denervate due to continued anterior horn cell or motor axon disease (denervation-reinnervation-denervation).

Changes Seen With Disuse of Muscle

When muscle strength is impaired secondary to problems remote from that muscle, such as upper motor neuron disease, disuse, corticosteroid use, polymyalgia rheumatica or collagen vascular disorders, selective atrophy of Type 2 muscle fibers occurs. This is a non-specific finding, which nevertheless, is commonly seen.
References


NERVE CONDUCTION STUDIES AND ELECTROMYOGRAPHY

Ralph F. Jozefowicz, MD

Nerve Conduction Study

Definition:

A nerve conduction study is the recording and measurement of the compound nerve and muscle action potential elicited in response to a single supramaximal electrical stimulus, to measure the terminal latency, amplitude and duration of the evoked potential, as well as the conduction velocity.

Both motor and sensory nerves can be studied. Typically, motor nerves are stimulated orthodromically (in the same direction as physiologic conduction), and this is accomplished by stimulating the nerve proximally and recording the compound muscle action potential distally.

Sensory nerves can be studied both orthodromically and antidromically (in the direction opposite to physiologic conduction for that fiber). Both orthodromic and antidromic stimulation of sensory nerves result in similar conduction velocities, but antidromic stimulation is typically performed as it is technically easier.

Technique:

Motor Nerves:

To perform motor nerve conduction studies, a surface electrode, the "active" electrode, is placed over the belly of a distal muscle that is innervated by the nerve in question. Another surface electrode, the "indifferent electrode", is placed distally over a distal joint. The nerve in question is then supramaximally stimulated with a stimulating electrode at a predetermined distance proximal to the active electrode and the resultant compound motor action potential (CMAP) is recorded. A supramaximal electrical stimulus is employed because one wishes to stimulate all of the nerve fibers in the nerve, and it is typically 20% greater than the stimulus required to achieve the largest CMAP.

Sensory Nerves:

To perform antidromic sensory nerve conduction studies, surface skin electrodes are placed over that portion of the skin innervated by the nerve in question. In the case of the upper extremity, ring electrodes that encircle the finger are typically used. As in motor nerve conduction studies, an "active" electrode and "indifferent" electrode are used, the indifferent electrode being placed distal to the active electrode. The sensory nerve in question is then supramaximally stimulated with a stimulating electrode at a predetermined distance proximal to the active electrode, and the resultant compound sensory nerve action potential (SNAP) is recorded.
Protocol:

Three parameters are routinely measured when performing nerve conduction studies, namely amplitude, terminal latency and conduction velocity.

1. **Amplitude**: The amplitude is the maximum voltage difference between two points, and is usually measured peak to peak. Amplitudes are routinely recorded for both compound muscle action potentials and sensory nerve action potentials, and are proportional to the number of available axons that are stimulated. Amplitudes are reduced in axonal neuropathies (neuropathies due to loss or damage of axons).

2. **Terminal Latency**: The terminal latency is the interval between the onset of a stimulus and the onset of the resultant compound muscle action potential or sensory nerve action potential. The sensory terminal latency has only one major component, namely the nerve conduction time from the stimulus point to the nerve terminal. On the other hand, the motor terminal latency has three components:

   - The nerve conduction time from the stimulus point to the nerve terminal.
   - Neuromuscular junction transmission time.
   - The time required to generate the muscle action potential.

Terminal latencies are prolonged in distal demyelinating neuropathies or in distal compressive neuropathies, such as carpal tunnel syndrome.

3. **Conduction Velocity**: The conduction velocity is the speed of propagation of an action potential along a nerve. The maximum conduction velocity is calculated from the latencies of the evoked potentials at supramaximal intensity of stimulation at two different points. The distance between the two points (conduction distance) is divided by the difference between the corresponding latencies (conduction time), resulting in a calculated velocity which represents the conduction velocity of the fastest fibers, and is expressed as meters per second:

\[
\text{Conduction velocity} = \frac{\text{Distance}}{\text{Time}}
\]

![Diagram of nerve conduction study](image_url)

**FIGURE 1**—Compound muscle action potential recorded from thenar eminence following stimulation of median nerve at elbow. Nerve conduction time from elbow to wrist can be determined as the latency difference between distal and proximal stimulations. Motor nerve conduction velocity (MNCV) is then calculated by dividing surface distance between stimulus points by latency difference.
The conduction velocity reflects the conduction in the largest, myelinated fibers only, and is slowed in demyelinating neuropathies, such as in Guillain-Barre Syndrome.

**Factors causing variability in normal nerve conduction studies:**

Four factors can influence normal nerve conduction studies, namely technique, limb temperature, portion of the nerve stimulated, and age of the patient.

1. **Technique:** Technical artifacts, namely precision in measurement of distances between stimulation points, precision in the placement of recording and stimulating electrodes, and accuracy in ensuring that a supramaximal electrical stimulus is used can all result in a falsely slowed nerve conduction velocity (up to 10 meters per second).

2. **Limb Temperature:** For every degree centigrade below 34, the nerve conduction velocity is slowed by 5%. Therefore, heat lamps should be used to ensure that limbs are at proper temperature during testing.

3. **Portion of Nerve Stimulated:** In general, proximal segments of nerves have faster conduction velocities than distal segments, as they are of larger diameter. In addition, conduction velocities in the arms are faster than in the legs, probably resulting from the temperature differences between these two limbs.

4. **Patient Age:** Infants have nerve conduction velocities that are 50% of normal. Adult values are not achieved until the age of 4 years.

**Abnormalities:**

- **Axonal Neuropathies:** Axonal neuropathies (neuropathies due to loss of axons or their cell bodies) generally result in a reduced amplitude of compound motor or sensory nerve action potentials.

- **Demyelinating Neuropathies:** Demyelinating neuropathies (neuropathies due to loss or destruction of myelin) result in slowed conduction velocities and prolonged terminal latencies, because conduction velocity is proportional to the velocity of the largest diameter, myelinated fibers.

- **Conduction Block:** Conduction block implies a failure of an action potential to be conducted past a particular point in the nerve, and is documented by demonstrating a reduction in amplitude of an evoked potential at two different stimulation points on a nerve trunk. Conduction block is usually seen with a severe focal compressive injury to a nerve.
Routine Nerves Studied:

Upper extremity:
- Median motor and sensory nerves.
- Ulnar motor and sensory nerves.

Lower extremity:
- Peroneal motor nerve.
- Tibial motor nerve.
- Sural sensory nerve.

Clinical usefulness of nerve conduction studies:

In general, nerve conduction studies are most helpful in evaluating polyneuropathies and compression neuropathies.

Polyneuropathies: Polyneuropathies can be axonal or demyelinating, and usually involve distal nerves symmetrically. In demyelinating polyneuropathies the terminal latencies are prolonged and the distal conduction velocities are slowed. In axonal neuropathies the amplitudes of the compound motor and sensory nerve action potentials are reduced. It is important to remember that few neuropathies are purely demyelinating or axonal, and most have mixed features. Also, severe axonal neuropathies can result in slowed distal conduction velocities, and severe demyelinating neuropathies can result in reduced amplitudes.
**Compression Neuropathies:** Compression neuropathies typically result in slowed conduction times and evidence for conduction block across the site of compression. Four compression neuropathies are commonly seen:

- **Carpal tunnel syndrome** - compression of the median nerve at the wrist.
- **Tardy ulnar palsy** - compression of the ulnar nerve across the elbow.
- **Peroneal nerve palsy** - compression of the peroneal nerve across the fibular head.
- **Tarsal tunnel syndrome** - compression of the tibial nerve at the ankle.

**F Wave and H Reflex**

**Definition:**

The F wave and H reflex are ways at looking at the conduction parameters for proximal portions of nerves, including the nerve roots.

**F Wave:**

The F wave is a late compound muscle action potential evoked intermittently from a muscle by a supramaximal electrical stimulus to the nerve. This late compound motor action potential occurs as a result of antidromic activation (backfiring) of alpha motor neurons. It has a variable latency and configuration, is small in amplitude and present only intermittently, and requires a supramaximal electrical stimulus in order to be elicited. F waves can be elicited from practically all distal motor nerves.

![Diagram of F Wave and H Reflex](image)

**FIGURE 1.** Eight consecutive tracings showing normal M responses and F waves with stimulation of ulnar nerve at wrist and elbow.

**FIGURE 2.**—Latency difference between F wave and M response representing passage of motor impulse to and from cord through proximal segment. Considering an estimated minimal delay of 1.0 ms at motor neuron pool, proximal latency from stimulus site to cord is expressed as \( \frac{F-M-1}{2} \) (msec), where F and M are latencies of F wave and M response, respectively. The FWCV in the segment to and from spinal cord is calculated as \( \frac{D \times 2}{D-F-M-1} \) (msec) where D is distance from stimulus site to cord and \( (F-M-1)/2 \), time required to cover length D. Ratio between conduction time in proximal segment to cord and that of remaining distal segment to muscle is calculated as follows: F ratio = \( \frac{F-M-1}{2M} \), where \( (F-M-1)/2 \) and M represent proximal and distal latencies, respectively.
H Reflex:

The H reflex is a late compound motor action potential that has a consistent latency and is evoked regularly from a muscle by a submaximal stimulus to a nerve. This compound motor action potential represents a spinal reflex and occurs as a result of stimulation of Ia afferent fibers. The H reflex has a consistent configuration and a large amplitude, and can only routinely be obtained from calf muscles with stimulation of the tibial nerve in the popliteal fossa.

FIGURE 3.—H reflex recorded from triceps surae after stimulation of the tibial nerve at knee. Shock intensity was gradually increased from subthreshold level (1) to supramaximal stimulation (8). Note initial increase and subsequent decrease in amplitude of reflex potential with successive stimuli of progressively higher intensity. H reflex normally disappears with shocks of supramaximal intensity that elicit maximal M response.
The following table compares characteristics of F waves and H reflexes:

<table>
<thead>
<tr>
<th>Attribute</th>
<th>F wave</th>
<th>H reflex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency</td>
<td>Late, variable</td>
<td>Late, consistent</td>
</tr>
<tr>
<td>Configuration</td>
<td>Variable</td>
<td>Constant</td>
</tr>
<tr>
<td>Amplitude</td>
<td>Small</td>
<td>Large</td>
</tr>
<tr>
<td>Stimulus</td>
<td>Supramaximal</td>
<td>Submaximal</td>
</tr>
<tr>
<td>Presence</td>
<td>Intermittent</td>
<td>Regular</td>
</tr>
<tr>
<td>Pathway</td>
<td>Backfiring of αMN</td>
<td>Spinal reflex</td>
</tr>
<tr>
<td>Distribution</td>
<td>All muscles</td>
<td>Calf muscles</td>
</tr>
</tbody>
</table>

**Electromyography**

**Definition:**

Electromyography (EMG) is the recording and study of insertional, spontaneous, and voluntary electrical activity of muscle. This test allows one to physiologically evaluate the motor unit, including the anterior horn cell, peripheral nerve, and muscle. EMG is helpful when evaluating patients with weakness, in that it can help one determine whether weakness is due to anterior horn cell disease, nerve root compression, peripheral neuropathy, or an intrinsic disease of muscle itself (myopathy).

**Technique:**

An EMG is performed by inserting a needle electrode into the muscle in question, and evaluating the compound motor action potentials both visually (on the oscilloscope screen) and aurally (over the loud speaker). Muscles are typically studied at rest and when voluntarily contracted.

Two types of electrodes are commonly used, monopolar and concentric.

- **Monopolar electrodes** record the potential between the bare tip of the electrode and a ground plate that is placed some distance from the electrode. Monopolar electrodes have a large recording area and are somewhat less uncomfortable than concentric electrodes.

- **Concentric electrodes** record the potential between the bare tip and shaft of the electrode. Concentric electrodes have a limited recording area and are somewhat more uncomfortable than monopolar electrodes. Both monopolar and concentric needle electrodes provide similar information, and the choice of electrodes depends upon the preference of the electromyographer.

**Protocol:**

When performing an EMG four parameters are studied, namely the insertional activity, spontaneous activity, voluntary activity and recruitment pattern.
1. **Insertional Activity:** This refers to the electrical response of muscle to the mechanical damage of needle movement, and consists of the electrical activity that is observed occurring within the first second of needle insertion. Insertional activity is typically brief in duration (0.5-1 second), but may be prolonged in acute neuropathies and active myopathies.

2. **Spontaneous Activity:** This refers to the action potential recorded from a muscle at rest after the insertional activity has subsided and when there is no voluntary contraction. Spontaneous activity may be normal or abnormal, as discussed below.

   - **Normal:** Normal spontaneous activity consists of the miniature end plate potentials (mEPP) that occur regularly at the neuromuscular junction. mEPP are referred to as "endplate noise" and reflect the spontaneous release of individual quanta of acetylcholine at the motor end plate.

   - **Abnormal:** Five forms of abnormal spontaneous activity can be seen, as follows:

     - **Fibrillations:** the electrical activity associated with fibrillating muscle fibers, reflecting the action potential of a single muscle fiber. These potentials usually occur repetitively and regularly, and are biphasic spikes of short duration with an initial positive phase and an amplitude of less than one millivolt.

     - **Positive sharp waves:** biphasic, positive-negative action potentials associated with fibrillating muscle fibers, and representing the discharge of a single muscle fiber.

   Fibrillations and positive waves have the same clinical significance, and only differ in configuration. Positive sharp waves occur when the electrode is recording from an area of damaged muscle. Fibrillations and positive sharp waves are both seen with acutely denervated muscle or with active (inflammatory) myopathies.

---

• **Fasciculation**: a sporadic, spontaneous action potential of a single motor unit associated with clinical fasciculation of muscle. Fasciculations usually occur as a result of discharge from an anterior horn cell or peripheral nerve. Fasciculations that occur occasionally are a normal phenomenon and are commonly associated with fatigue. Continuous, widespread fasciculations associated with muscle weakness are suggestive of anterior horn cell disease (ALS).

• **Myotonic discharge**: a repetitive discharge of biphasic spike potentials recorded after needle insertion or following muscle percussion, in which the amplitude and frequency of the potentials must both wax and wane. This change produces a characteristic musical sound on the loudspeaker, likened to the sound of a "dive bomber". Myotonic discharges are frequently seen in the myotonic disorders, including myotonic dystrophy and congenital myotonia.

![Diagram of fasciculation](image)

• **Complex repetitive discharge**: a polyphasic action potential that may begin spontaneously or after needle movement, and which has a uniform frequency, shape and amplitude with abrupt onset, cessation, or change in configuration. Complex repetitive discharges are nonspecific findings that can be seen in neuropathic or myopathic disorders.

3. **Voluntary Activity**: the electrical activity recorded from a muscle with consciously controlled muscle contraction. This activity normally consists of compound muscle action potentials (i.e. the sum of the action potentials of all muscle fibers innervated by a single anterior horn cell).

Motor unit potentials are evaluated as to their amplitude, duration, and presence or absence of *polyphasia* (five or more crossings of the baseline).

Normal motor unit potentials have an amplitude between 0.3 and 1.5 millivolts, a duration between 10 and 20 milliseconds, and fewer than four phases (crossings of the baseline).
Abnormal motor unit potentials are of two types, neuropathic and myopathic:

- **Neuropathic potentials** have a large amplitude and long duration, and are frequently polyphasic, since neuropathic potentials reflect enlarged motor units due to reinnervation of previously denervated muscle fibers.
Myopathic potentials are of low amplitude, short duration and are frequently polyphasic as well, since the motor units have become smaller in size because of a drop-out of individual muscle fibers as a result of muscle disease.

Volume conduction represents the spread of current from a potential source through a conducting medium, such as body tissue, and results in poorly defined motor unit potentials that have a muffled sound. Volume conduction implies that the electrode is incorrectly positioned in the muscle fiber with respect to the portion of the muscle fiber that is being activated.

4. Recruitment: The initiation of firing of additional motor units as those active increase their rate of discharge. To test for recruitment, the patient is asked to maximally contract the muscle that is being sampled. As the strength of contraction increases, two physiologic processes occur in an orderly fashion, namely an increase in the rate of firing of the motor units that are already discharging, and a recruitment of additional motor units.

Abnormal recruitment is seen in two settings, namely in chronic myopathies and chronic neuropathies.

- In chronic myopathies recruitment is rapid, since the brain compensates for loss of muscle power from muscle disease by bringing all the motor units into play at low levels of force.

- In chronic neuropathies recruitment is reduced, since the total number of available motor units is reduced in this setting. In severe chronic neuropathies, with maximal levels of force, only one rapidly firing motor unit is sometimes observed in the area of muscle that is being sampled.
Pathologic Findings:

Myopathies:

- Active (inflammatory) myopathies: fibrillations and positive waves are present with the muscle at rest.

- Chronic myopathies: voluntary motor unit potentials are of low amplitude and short duration and are frequently polyphasic. Recruitment may be rapid.

**Figure 13-3**

Typical findings in myogenic lesions. They include (1) normal insertional activity; (2) no spontaneous activity, although there are some notable exceptions; (3) low amplitude, short duration, polyphasic motor unit potentials; and (4) early recruitment leading to low amplitude, full interference pattern at less than maximal effort of contraction. The diagram illustrates random loss of individual muscle fibers resulting in reduced number of fibers per motor unit.
Neuropathies:

- **Acute denervation**: fibrillations and positive waves are present, indicating spontaneous discharge of individual muscle fibers.

- **Chronic neuropathy**: voluntary motor unit potentials are of large amplitude and long duration and are frequently polyphasic, because the motor units are enlarged as a result of reinnervation of adjacent previously denervated muscle fibers. Recruitment is reduced for the same reason.

![Lower Motor Neuron Lesion Diagram]

**Figure 13-1**

Typical findings in lower motor neuron lesions. They include (1) increased insertional activity; (2) spontaneous activities in the form of fibrillation potentials and positive sharp waves, (3) large amplitude, long duration polyphasic motor unit potentials; and (4) discrete single unit activity firing rapidly during maximal effort of contraction. The diagram illustrates denervation and reinnervation of a group of muscle fibers supplied by a diseased axon. (Compare Figure 12-1.)
Clinical Applications:

- **Myopathies:** EMGs are helpful in differentiating active (inflammatory) myopathies from chronic myopathies. The active myopathies include dermatomyositis, polymyositis, and some forms of muscular dystrophy such as Duchenne muscular dystrophy. The chronic myopathies include the other muscular dystrophies, the congenital myopathies, and some metabolic myopathies. Myotonic muscular dystrophy and congenital myotonia produce characteristic myotonic discharges.

- **Neuropathies:** EMG can differentiate acute denervation from chronic denervation, and may thus give an indication as to the time course of the lesion causing the neuropathy. In addition, based on which muscles have an abnormal EMG pattern, one can determine whether the neuropathy is due to a lesion of a nerve root (radiculopathy), the brachial or lumbosacral plexus (plexopathy), an individual peripheral nerve (mononeuropathy), or multiple peripheral nerves (polyneuropathy).

The following table summarizes some of the abnormal EMG findings seen in various neuromuscular disorders:

<table>
<thead>
<tr>
<th>EMG FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lesion</strong></td>
</tr>
<tr>
<td><strong>EMG Steps</strong></td>
</tr>
<tr>
<td>Insertional Activity</td>
</tr>
<tr>
<td>Spontaneous Activity</td>
</tr>
<tr>
<td>Motor Unit Potential</td>
</tr>
<tr>
<td>Interference Pattern</td>
</tr>
</tbody>
</table>

Typical findings in lower and upper motor neuron disorders and myogenic lesions as shown in Figures 13-1 through 13-3. Myotonia shares many features common to myopathy in general but is additionally characterized by myotonic discharges triggered by insertion of the needle and with voluntary effort to contract the muscle. Polymyositis shows combined features of myopathy and neuropathy, including (1) increased insertional activity; (2) abundant spontaneous discharges; (3) small amplitude, short duration, polyphasic motor unit potentials; and (4) early recruitment leading to low amplitude, full interference pattern.
References


MOTOR NEURON DISEASES

Ralph F. Józefowicz, MD
Denise Figlewicz, Ph.D.

The motor neuron diseases are a group of disorders characterized by selective deterioration of upper and/or lower motor neurons. The following table lists the spectrum of motor neuron diseases:

<table>
<thead>
<tr>
<th>LMN Signs</th>
<th>LMN &amp; UMN Signs</th>
<th>UMN Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Muscular Atrophy</td>
<td>Amyotrophic Lateral Sclerosis</td>
<td>Lateral Sclerosis</td>
</tr>
<tr>
<td>- Infantile (Werdnig-Hoffman)</td>
<td>(Motor Neuron Disease)</td>
<td></td>
</tr>
<tr>
<td>- Intermediate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Juvenile (Kugelberg-Welander)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Adult (Aran-Duchenne)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Progressive Bulbar Palsy</td>
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</tr>
</tbody>
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SPINAL MUSCULAR ATROPHIES

The spinal muscular atrophies are a group of motor neuron diseases characterized by degeneration of anterior horn cells and some cranial motor nerve nuclei that result in progressive, generalized weakness of limb, trunk and bulbar musculature, muscular atrophy, fasciculations and hyporeflexia. Recently, the abnormal gene responsible for the childhood forms of spinal muscular atrophy has been localized to chromosome 5. Each of the various spinal muscular atrophies has a specific age of onset, as noted in the table below:

**THE SPINAL MUSCULAR ATROPHIES**

<table>
<thead>
<tr>
<th>Age of Onset</th>
<th>Inheritance Pattern</th>
<th>Course</th>
<th>Muscle Biopsy</th>
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<tr>
<td>Infantile</td>
<td>3-6 mos. AR</td>
<td>Death by age 2-3 years from respiratory failure</td>
<td>Sheets of round atrophic fibers</td>
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<td>(Werdnig-Hoffman)</td>
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<tr>
<td>Intermediate</td>
<td>18 mos. AR</td>
<td>Less rapid</td>
<td>Fiber type grouping</td>
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<tr>
<td>Juvenile</td>
<td>5-15 yrs. AR, Sporadic</td>
<td>Slowly progressive</td>
<td>Atrophic fibers, Fiber type grouping</td>
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<td>(Kugelberg-Welander)</td>
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<tr>
<td>Adult</td>
<td>&gt;20 yrs. Sporadic</td>
<td>Variable</td>
<td>Atrophic fibers, Fiber type grouping</td>
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<tr>
<td>(Aran-Duchenne)</td>
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Infantile Spinal Muscular Atrophy  
(Werdnig-Hoffman Disease)

This form spinal muscular atrophy has an autosomal recessive pattern of inheritance. Signs of the disease may be present at birth, or may become noticeable several weeks later. At any rate, the symptoms are well developed by 3-6 months of age. The clinical signs include marked weakness of limb muscles, bulbar muscles with subsequent feeding difficulties, and respiratory distress. The extraocular muscles are not affected. Tongue fasciculations are seen in half of the patients. The disease is rapidly progressive, with death due to respiratory failure by 2-3 years of age. The etiology of this disorder is unknown.

Muscle biopsy is quite characteristic, with sheets of round, atrophic fibers intermingled with groups of markedly hypertrophic fibers. The hypertrophic fibers tend to be almost all Type 1 fibers. Muscle enzymes, including creatine kinase (CK) are slightly increased. EMG reveals fibrillations at rest. There is no effective treatment.

Intermediate Spinal Muscular Atrophy

This disorder is also autosomal recessive in inheritance. Onset of this disorder is at approximately 18 months. The clinical features are similar to that of infantile spinal muscular atrophy, although the course is less rapid. As the disease progresses, skeletal deformities develop, most commonly kyphoscoliosis. Contractures of hip and knee joints are also seen.

The muscle biopsy in this disorder also shows sheets of round atrophic fibers, but fiber type grouping is also seen, indicative of chronic denervation. Muscle enzymes, including CK, and EMG findings are similar to that found in infantile spinal muscular atrophy. No effective treatment is available, although aggressive physical therapy is quite helpful in preventing joint contractures and possibly scoliosis. Vigorous pulmonary toilet may prevent some respiratory complications.

Juvenile Spinal Muscular Atrophy  
(Kugelberg-Welander Disease)

The onset of this disorder is later than in the previous two diseases, with onset between the ages of 5-15 years. An autosomal recessive pattern is frequently seen, although sporadic cases are common as well. The disease begins gradually with slowly progressive proximal muscle weakness. Pseudohypertrophy of the calf muscles is seen in some patients. Many of these patients remain ambulatory into adult life. Serum muscle enzymes are elevated, and EMG reveals signs of denervation, as in the other spinal muscular atrophies.

The muscle biopsy reveals large numbers of atrophic fibers occurring both randomly and in small groups, as well as fiber type grouping. Treatment consists of physical therapy and pulmonary toilet.
Adult Spinal Muscular Atrophy 
(Aran-Duchenne Disease)

This is a rare form of spinal muscular atrophy with onset in adult years. It is almost always sporadic. The clinical course is variable, rapidly progressive in some, and protracted in others. The muscle biopsy shows signs of both acute and chronic denervation, including atrophic fibers and fiber type grouping. Only supportive therapy is available.

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (motor neuron disease) is a progressive disorder of unknown etiology, characterized by degeneration of upper motor neurons, certain cranial motor nerve nuclei and anterior horn cells, that results in diffuse muscle weakness and wasting, spasticity, hyperreflexia and bulbar dysfunction.

Incidence

- 1-2 per 100,000
- Seen more frequently in males, with a ratio of 1.8 to 1
- Seen most often in older persons, with a median age of onset of 66 years
- Usually sporadic, although 5-10% of patients have a positive family history

Clinical Aspects

The symptoms of ALS are associated with degeneration of all motor neurons throughout the nervous system, including upper motor neurons, lower motor neurons, and brain stem motor neurons.

- **Lower motor neuron findings:** Degeneration of anterior horn cells leads to muscle atrophy, weakness, fasciculations, hyporeflexia, and leg cramps.

- **Upper motor neuron findings:** Degeneration of large pyramidal cells in the motor cortex results in spasticity, hyperreflexia, and positive Babinski responses.

- **Bulbar findings:** Degeneration of lower brain stem motor neurons results in dysphagia, dysarthria, pseudobulbar affect, as well as tongue fasciculations.

Despite the widespread involvement of motor neurons, certain muscle groups are rarely involved. These include the extraocular muscles, the bowels and bladder.

Damage to other areas of the nervous system is not typical of this disease. Accordingly, sensory abnormalities, problems with mentation and autonomic function are usually preserved.
Course:

In most cases, ALS is a rapidly progressive disease. The majority of patients are dead to due respiratory failure within 3 years of diagnosis. However, it is not unusual to see patients with this disorder live for 10 or more years, having plateaued at some point in their course.

Diagnosis

The diagnosis of ALS is mainly a clinical diagnosis, although laboratory data is often quite helpful in confirming the diagnosis and ruling out other diagnoses.

- **Clinical exam:** The diagnosis of ALS can be made with some assurance if weakness, wasting, fasciculations and hyperreflexia are found in 3 or more limbs. If bulbar difficulties are also seen, the diagnosis is even more likely.

- **Muscle enzymes:** Creatine kinase (CK) is often increased 2-3 fold in this disorder.

- **EMG:** EMG shows widespread fibrillations associated with giant polyphasic potentials and fasciculations. These abnormalities should be present in 3 or more limbs.

- **Muscle biopsy:** Muscle biopsy findings include signs of both recent and chronic denervation, including atrophic fibers and fiber type grouping. In addition, hypertrophy of Type 2 fibers is commonly seen for unclear reasons.

Differential diagnosis:

Although ALS is often easy to recognize, certain other illnesses with far better prognoses may mimic some of the changes of ALS, and should always be considered in the differential diagnosis. Cervical spine disease, with cord compression leading to upper motor neuron signs in the legs, and nerve root compression leading to lower motor neuron signs in the arms, needs to be ruled out, and radiologic studies, including cervical myelography or magnetic resonance imaging, should be obtained in all questionable cases.

Etiology and Pathogenesis

The etiology and pathogenesis of ALS is most likely a stage-like process:

**Original insult(s) → Disease propagation → Motor neuron death**

There is very little established evidence concerning the original insult to motor neurons in ALS. ALS is inherited in approximately 10% of cases, and therefore gene mutations will be the direct cause in these patients. 15% of inherited cases of ALS are due to mutations in the Cu, Zn superoxide dismutase gene (SOD-1) on chromosome 21. The identity of genes accounting for the remainder of inherited cases should be known within the next few years.
The majority of ALS cases are sporadic. A number of hypotheses have emerged within the past 40 years, yet none has been validated as a cause. Many of the hypotheses have been based on properties of the motor neurons themselves:

- The lower motor neuron is a very large neuron with high metabolic demands (lifelong generation of high levels of oxidative free radicals, and needing many mitochondria to generate ATP). Lower motor neurons have processes that can measure a meter in length (demand for effective axonal transport and an intact neuronal cytoskeleton).

- Lower motor neurons have access to the periphery via the neuromuscular junction (a potential source of metabolic or environmental toxins, or a loss of important neurotrophic factors, which can be retrogradely transported to the motor neuron cell body).

- Both upper and lower motor neurons have a strong electrophysiological excitatory bias and receive high levels of input through glutamate receptors. Moreover, in comparison to neuronal populations that do not die in ALS, they lack intracellular calcium-binding proteins that might compensate for calcium influx through these glutamate receptors. Infectious and viral mechanisms of ALS have been sought but to date, no virus has been strongly associated with ALS.

Recent reports have noted an association between poliomyelitis and ALS. Both of these diseases show a predilection for anterior horn cells, and some patients who have had poliomyelitis may develop a chronic progressive form of motor neuron disease after many years. This "post-polio syndrome" of progressive weakness may have a common-sense explanation. Most muscles have so much reserve function that 25% may be lost without the patient being aware of any weakness. A muscle that has been previously affected by poliomyelitis has no such reserve. Thus, any loss of motor neurons as seen in normal aging, will have a more profound effect on any limbs weakened by previous poliomyelitis. Thus, the "post-polio syndrome" may simply represent an aging phenomenon.

Current thinking about ALS is that a number of different insults may serve as the primary problem in different individuals, including the hypothetical causes described above, as well as others.

A new focus of attention is the concept of "spread" of symptoms, and hence underlying motor neuron degeneration, from one population of motor neurons to those in an anatomically adjacent region. The presence of gliosis in postmortem ALS spinal cord was demonstrated a long time ago; however the creation of good transgenic animal models of ALS has now allowed the study of chronic progressive motor neuron disease in presymptomatic patients and in early stages of degeneration. Recent studies using one such model report up-regulation of pro-inflammatory factors in presymptomatic stages, and subsequent immune activation accompanying motor neuron damage in the anterior horn of the spinal cord. Hence, inflammatory mechanisms should now be considered as one contributor to motor neuron disease progression.
The ultimate death of motor neurons, following a number of primary upstream insults, has been shown in studies from many laboratories to be directly related to stimulation of non-NMDA type glutamate receptors (also referred to as AMPA/kainate receptors) and the subsequent influx of calcium into the neuron. This may lead to apoptotic or necrotic cell death pathways. The drug riluzole probably acts to block or retard this excitotoxic cell death.

Treatment “cocktails” are now being considered for clinical trial, using therapeutic agents that target putative processes in all three of these disease stages, as well as symptomatic intervention.

Treatment

There is no proven cure for ALS. Nonetheless, the physician has an important role in the treatment of this disorder. Providing emotional support and coordinating symptomatic care are crucial in chronic progressive illnesses.

Physical therapy, including range of motion exercises to prevent joint contractures, can help in maintaining mobility and reduce discomfort. Walkers, raised toilet seats, wheelchairs and braces are also important in providing a measure of independence.

Vigorous pulmonary toilet as well as oral suctioning can prevent respiratory complications of this disorder. In patients with significant dysphagia that can progress to inanition and weight loss, placement of a feeding gastrostomy tube may be helpful. There is certainly much to be said for this procedure in patients whose meal times are spent in paroxysms of choking.

Finally, some patients with terminal respiratory insufficiency may elect to undergo tracheostomy and be placed on home mechanical ventilatory support. This is a very personal issue that is decided on by the patient, his family, and his physicians. We have had several patients who have done relatively well at home for a number of years with mechanical home ventilation.

Several medications have been found to be helpful in ameliorating some of the symptoms of ALS. Quinine and diazepam, when given at bedtime, are often helpful in treating nocturnal leg cramps. Also, amitriptyline (Elavil) has been found to be very effective in treating emotional incontinence seen with pseudobulbar palsy.

Riluzole, an antiglutamate agent, has been reported to be the first effective treatment for ALS. This drug slowed the progression of ALS over a 21 month follow-up period when compared with placebo. Since the one-year survival rates increased primarily in the subgroup of patients with bulbar-onset disease, the effectiveness of riluzole for ALS patients with limb-girdle-onset disease remains in doubt.
REFERENCES


PERIPHERAL NEUROPATHY
Ralph F. Józefowicz, MD

Peripheral neuropathy is a general term for any disorder affecting the peripheral nerves. Since peripheral neuropathy can be caused by numerous factors, an investigation into the cause of the neuropathy should be undertaken as soon as the diagnosis of neuropathy is made.

CLINICAL FEATURES

Symptoms

Since the peripheral nervous system consists of motor, sensory and autonomic nerves, symptoms can fall into all three of these categories.

- **Sensory symptoms** include distal dysesthesias, pain and numbness. A characteristic pattern of numbness is one in which the distal portions of the nerves are first affected, the so-called "stocking-glove" pattern. This pattern occurs because nerve fibers are affected according to length of axon, without regard to root or nerve trunk distribution.

- **Motor symptoms** include weakness, which once again is distal, and typically involves extensor groups rather than flexor groups of muscles.

- **Autonomic dysfunction** is common and includes orthostasis, impotence in males and gastroparesis.

Signs

Signs of peripheral neuropathy also include sensory, motor and autonomic components.

- **Sensory disturbance** is manifest as distal loss of pin, temperature and vibratory perception as well as proprioception. Initial signs are frequently confined to the toes and feet. A **positive Romberg sign** is frequently present due to proprioceptive loss in the lower extremities.

- **Motor signs** include distal weakness, primarily in extensor groups, and most prominent in the lower extremities initially. Distal muscles are often atrophic, and one should carefully assess the bulk of the extensor digitorum brevis muscles in the feet and of the intrinsic muscles of the hands. Muscle tone is reduced and often is flaccid.

- **Muscle stretch reflexes** are frequently lost, and most patients with peripheral neuropathy have **absent ankle jerks** as one of the first signs of the disorder.

- The most prominent **autonomic sign** of neuropathy is orthostatic hypotension.
CLASSIFICATION

There are many ways to classify peripheral neuropathy. One helpful method is to consider four categories, namely etiology, distribution, pathology and modality.

Etiology

Most peripheral neuropathies fall into three etiologic categories, namely hereditary, toxic/metabolic, and those associated with systemic disease.

Hereditary:

This is a large group of disorders in which the onset of symptoms is insidious and progression is indolent over years or decades. Three of these hereditary neuropathies will be discussed:

- **Charcot-Marie-Tooth Disease** (Hereditary Sensory-Motor Neuropathy [HSMN] I). This is the most common hereditary neuropathy that has an autosomal dominant pattern of inheritance. Phenotypic expression is often variable, such that affected family members of a propositus may have no symptoms and minimal neurologic findings. Characteristic clinical findings include striking atrophy of the calves, resulting in an inverted "champagne-bottle" appearance to the lower extremities. Peripheral nerves are often palpably enlarged. Large fiber sensory loss is present, with a marked reduction in vibratory perception and proprioception. Ankle jerk reflexes are lost. Since this is a demyelinating polyneuropathy, nerve conduction velocity measurements are characteristically slow, at approximately 50% of normal values.

- **Dejerine-Sottas Disease** (HSMN III). This is a rare pediatric disorder with autosomal recessive inheritance that causes severe weakness and numbness, markedly enlarged peripheral nerves with "onion-bulb" formation and markedly slowed conduction velocities.

- **Refsum's Disease** (HSMN IV). This autosomal recessive disorder is caused by an enzymatic defect that results in accumulation of phytanic acid. The clinical triad includes peripheral neuropathy, retinitis pigmentosa and dry, scaly skin. Treatment includes dietary restriction of phytanic acid and plasmapheresis.

Toxic/Metabolic:

Numerous drugs and toxins can cause peripheral neuropathy. A partial list follows:

- **Drugs**: amiodarone, cis-platinum, dapsone, INH, phenytoin, pyridoxine, vincristine, nitrofurantoin, ddI, ddC.

- **Toxins**: heavy metals including mercury, arsenic, lead, zinc and thallium; alcohol; and the organophosphates.
Neuropathy Associated with Systemic Diseases:

- Numerous systemic diseases are associated with neuropathy. Among the most common systemic disorders are: uremia; porphyria; vitamin B<sub>12</sub> deficiency; amyloidosis; hypothyroidism; lymphoma, including Hodgkin's disease; multiple myeloma; cryoglobulinemia; vasculitis, including systemic lupus erythematosus (SLE), rheumatoid arthritis and polyarteritis nodosa; sarcoidosis; and benign monoclonal gammopathy, including IgG, IgA and IgM.

- A purely sensory neuropathy can be seen with several carcinomas, especially oat cell carcinoma of the lung.

- Four systemic infections have a high incidence of neuropathy, including leprosy, syphilis, HIV and diphtheria.

- Diabetes mellitus is perhaps the most common cause of neuropathy in the United States. Both symmetric and asymmetric diabetic neuropathies can occur, as follows:
  - **Symmetric polyneuropathies**: These are the most common and include a sensory/motor polyneuropathy and an autonomic neuropathy.
  - **Asymmetric neuropathies** are less common. Mononeuropathy multiplex results in simultaneous dysfunction of several peripheral nerves, and is due to ischemic infarction of the vasa nervorum. Cranial neuropathies, truncal radiculopathies and diabetic amyotrophy (ischemic infarction of the lumbosacral plexus) are other forms of asymmetric neuropathies. Entrapment neuropathies, including carpal tunnel syndrome, are also commonly seen in diabetics.

Distribution

Nerve damage in peripheral neuropathy may be symmetrical generalized, multifocal or focal.

- **Symmetrical generalized polyneuropathies** produce signs and symptoms in a distal-to-proximal gradient, the so-called "stocking-glove" pattern. The reason for this is that the "offending agent" causing the neuropathy affects protein synthesis in the cell body of the peripheral nerve. Hence, neuronal dysfunction will first occur in the distal portions of the longest axons, and thus produce symptoms of weakness and numbness in the most distal portions of the extremities, i.e. the feet and hands.

- **Multifocal Neuropathies (Mononeuropathy Multiplex)**: Patients with these forms of neuropathy develop more-or-less simultaneous dysfunction of several peripheral nerves. The underlying pathologic mechanism is felt to be ischemic infarction of the vasa nervorum due to vasculitis, as can occur with SLE, rheumatoid arthritis, polyarteritis nodosa and diabetes mellitus. These neuropathies are frequently painful and cause profound weakness. Prognosis for recovery is good, assuming that the underlying disease process leading to nerve infarction can be suppressed.
• **Focal Neuropathies (Mononeuropathies):** Traumatic injuries and entrapment of peripheral nerves at the usual sites of compression are the most common causes of focal mononeuropathy. The most frequently seen entrapment neuropathies include:

  - Compression of the median nerve across the wrist (carpal tunnel syndrome)
  - Compression of the ulnar nerve across the elbow (tardy ulnar palsy)
  - Compression of the radial nerve at the spiral groove (Saturday night palsy)
  - Compression of the peroneal nerve at the fibular head (peroneal nerve palsy)
  - Compression of the distal branches of the tibial nerve at the ankle (tarsal tunnel syndrome)

**Pathology**

There are three major pathologic mechanisms causing peripheral neuropathy: distal axonopathy, myelinopathy, and neuronopathy.

**Distal Axonopathy:**

In this form of neuropathy, a metabolic abnormality causes failure of protein synthesis and axonal transport, resulting in degeneration of distal regions of axons. For this reason, axonal neuropathies characteristically produce a "stocking-glove" distribution of numbness and weakness.

Small-diameter axons are most susceptible to metabolic injury because of their small neuronal size and lack of "reserve". Hence, initial symptoms of an axonal neuropathy typically include autonomic dysfunction and small-fiber sensory modalities, including loss of pain and temperature perception, since these modalities are subserved by small, unmyelinated or thinly myelinated axons.

**Myelinopathy:**

An immune-mediated attack on peripheral nervous system myelin is the characteristic pathologic change in this group of neuropathies. Guillain-Barre syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) are the two most common forms of demyelinating polyneuropathy.

GBS is a monophasic, immune-mediated demyelinating neuropathy that frequently follows a viral infection and causes an acute and frequently severe progression of weakness and numbness over several weeks. CIDP is a chronic demyelinating polyneuropathy that can have a slowly progressive or a relapsing course. In both of these neuropathies antibodies have been found that cross-react with peripheral nerve myelin. Elevated CSF protein and slowed nerve conduction velocities are characteristic of the demyelinating neuropathies.

In general, demyelinating neuropathies affect large-diameter, myelinated axons at the start of the illness, and hence produce significant motor weakness and large-fiber sensory loss, including loss of vibratory perception and proprioception.
In diphtheritic neuropathy, the bacterium produces a toxin that inhibits Schwann cell synthesis of myelin constituents, producing severe weakness and large-fiber sensory loss.

Neuronopathy:

Selective involvement of the cell bodies of motor, sensory and autonomic nerves is the hallmark of this group of neuropathies.

- **Somatic motor neuronopathies** result from isolated involvement of the anterior horn cells. Amyotrophic lateral sclerosis and the spinal muscular atrophies are two examples of somatic motor neuronopathies.

- **Somatic sensory neuronopathies** result from disruption of the metabolism of sensory nerve cell bodies, followed by degeneration of their processes. Special permeability of the blood vessels in the dorsal root and Gasserian ganglia make these neurons particularly vulnerable to certain toxins. Two common examples of somatic sensory neuronopathies include the paraneoplastic subacute sensory neuropathy seen with oat-cell carcinoma of the lung, and the sensory neuronopathy associated with Sjogren's syndrome.

- **Autonomic Neuronopathy:** This unusual group of neuropathies results from isolated involvement of post-ganglionic autonomic neurons and causes idiopathic orthostatic hypotension.

**Modality**

Peripheral neuropathies can be sub-classified based on their involvement of motor, sensory or autonomic neurons.

- **Modality-Specific Neuropathies:** The somatic motor, somatic sensory and autonomic neuronopathies described above are examples of modality-specific neuropathies. The pathologic lesion in this group of neuropathies is confined to the cell bodies.

- **Mixed-Modality Neuropathies:** The majority of peripheral neuropathies is not modality-specific, and includes various combinations of motor, sensory and autonomic dysfunction. The reason for this finding is that most peripheral nerves include a mixture of motor, sensory and autonomic axons. Hence, axonal neuropathies typically present with mixed symptomatology. Likewise, since most axons are myelinated to a greater or lesser extent, demyelinating neuropathies also produce a mixture of motor, sensory and autonomic symptoms.
The mnemonic **DANG THERAPIST** is helpful in recalling the more common causes of peripheral neuropathy:

- Diabetes Mellitus
- Alcohol
- **Nutritional** (B₁₂ deficiency)
- Guillain-Barre Syndrome
- Toxins (Pb, As, Zn, Hg)
- Hematologic (paraproteins)
- Endocrine (hypothyroid)
- Rheumatologic (SLE, rheumatoid arthritis, vasculitis)
- Amyloid
- Porphyria
- Infectious (syphilis, HIV)
- Sarcoid
- Tumor (paraneoplastic neuropathy)

**LABORATORY INVESTIGATION**

Laboratory studies play an important role in diagnosing and categorizing the peripheral neuropathies. Electrodiagnostic studies are helpful in quantitating the neuropathy, while blood and urine studies are helpful in identifying an etiology.

**Electrodiagnostic Studies**

**Nerve Conduction Study:**

The recording and measurement of the compound nerve and muscle action potential elicited in response to a single supramaximal electrical stimulus, to measure the terminal latency, amplitude and duration of the evoked potential, as well as the conduction velocity.

Nerve conduction studies are helpful in documenting that a neuropathy exists, quantitating the severity, and noting the distribution of the neuropathy, i.e. whether it is distal, proximal or diffuse. In addition, nerve conduction studies can provide information on the modality involved, i.e. motor versus sensory, and can also give clues as to the underlying pathology, whether axonal or demyelinating.

**Demyelinating neuropathies** (neuropathies due to loss or destruction of myelin) result in **slowed conduction velocities** and **prolonged distal latencies**, because conduction velocity is proportional to the velocity of the largest-diameter myelinated fibers. **Dispersion of evoked compound action potentials (CAP)** can also be seen in demyelinating neuropathies, because all of the action potentials elicited in response to a single electrical stimulus will not reach the recording potential at the same time.
Severe demyelinating neuropathies can also produce conduction block, which is a major decrease in amplitude of the muscle CAP upon proximal stimulation of its nerve as compared to distal stimulation.

Axonal neuropathies (neuropathies due to loss of axons or their cell bodies) generally result in a reduced amplitude of the compound motor or sensory nerve action potentials.

Electromyography (EMG):

The recording and study of insertional, spontaneous, and voluntary electrical activity of muscle.

This test allows one to physiologically evaluate the motor unit, including the anterior horn cell, peripheral nerve, and muscle. EMG is helpful when evaluating patients with weakness, in that it can help one determine whether weakness is due to anterior horn cell disease, nerve root compression, peripheral neuropathy, or an intrinsic disease of muscle itself (myopathy).

EMG can differentiate acute denervation from chronic denervation, and may thus give an indication as to the time course of the lesion causing the neuropathy.

- **Acute Denervation**: Fibrillations and positive waves are present indicating spontaneous discharge of individual muscle fibers.

- **Chronic Denervation**: Voluntary motor unit potentials are of large amplitude and long duration, and are frequently polyphasic, because the motor units are enlarged as a result of re-innervation of adjacent previously denervated muscle fibers. Recruitment of additional motor units in response to increasing the force of muscular contraction is reduced for the same reason.

- **Demyelinating Neuropathy**: A decreased recruitment pattern is seen, since demyelination interferes with conduction of individual action potentials along the course of a peripheral nerve. Because denervation and reinnervation of muscle fibers are not features of demyelinating neuropathies, the configuration of the voluntary motor unit potentials is usually normal, and fibrillation potentials are not seen.

**Nerve Biopsy**

There are few indications for nerve biopsy when evaluating peripheral neuropathy. In general, a nerve biopsy is performed to evaluate asymmetric, multi-focal neuropathies. The sural nerve is frequently biopsied, since this is a purely sensory nerve that is easily obtained. In the upper extremity, the superficial radial nerve may be biopsied if necessary.

The nerve specimen is typically evaluated by means of light and electron microscopy. Semi-thin plastic embedded sections, stained with toluidine blue, are helpful for evaluating the myelin sheaths. Teased nerve fiber preparations are also helpful to look for demyelination and remyelination.
Sural nerve biopsies are particularly helpful when evaluating patients with a clinical picture of mononeuropathy multiplex, the basis of which is still unclear after other laboratory investigations are complete. Vasculitis, amyloidosis, leprosy and sarcoidosis can be accurately diagnosed by means of nerve biopsy.

Performing a nerve biopsy routinely in the evaluation of symmetric, distal polyneuropathies is usually fruitless, in that the pathologic diagnosis most often reveals "chronic neuropathy with mixed axonal-demyelinating features", a non-specific finding of little clinical benefit.

**Blood Studies**

Routine blood studies should be obtained in all patients with peripheral neuropathy in order to screen for reversible causes. The following blood tests are recommended:

- Complete blood count
- Chemistry profile
- Sedimentation rate
- Thyroid studies
- Vitamin B<sub>12</sub> level
- ANA, rheumatoid factor
- Serum protein electrophoresis, serum immuno-electrophoresis
- RPR and HIV (if the clinical situation warrants)

**Urine Studies**

The following studies are recommended to screen for reversible causes of neuropathy:

- Heavy metal screen (Hg, Pb, Zn, As)
- Urine protein electrophoresis, urine immuno-electrophoresis
- Watson-Schwartz test (qualitative test for porphobilinogen)

Chest x-ray, helpful to screen for asymptomatic lung cancer that can sometimes cause a purely sensory neuropathy.

**TREATMENT**

**Neuropathy Associated With Systemic Illness**

Treatment of the systemic illness frequently results in improvement in neuropathic symptoms. Since nerves regenerate slowly, at a rate of about one mm per day, recovery is often prolonged and may take months to years.
Immune-mediated Neuropathies

The immune-mediated neuropathies include those associated with vasculitis (SLE, rheumatoid arthritis or polyarteritis nodosa), and the immune-mediated demyelinating neuropathies (Guillain-Barre syndrome and CIDP).

Corticosteroids:

By virtue of their immunosuppressive effects, corticosteroids have been found to be effective in treating the vasculitic neuropathies as well as CIDP. Corticosteroids may be given daily or on an every-other-day regimen, depending on the severity and tempo of the disease. The typical initial dose of corticosteroids for the treatment of these neuropathies is 1 mg/kg/day of prednisone (or 2 mg/kg every-other-day).

Corticosteroids have never been proven to be effective in treating Guillain-Barre syndrome, and hence are not recommended for this disorder.

Immunosuppressives:

Azathioprine, cyclophosphamide, cyclosporine, and methotrexate are all used in the treatment of autoimmune diseases. Each of these medications has potential serious toxicity.

Azathioprine is frequently used, in combination with steroids, to treat autoimmune neuropathies because of its steroid-sparing effect. Concurrent use of these two medications allows corticosteroids to be tapered more quickly and more completely once the neuropathy is brought under control.

The usual dosage of azathioprine is 2-3 mg/kg/day given in divided doses. This medication has a delayed beneficial effect and several months are required before an effect may be seen. The erythrocyte mean cell volume (MCV) provides an index of therapeutic effect: a slight elevation in MCV suggests that the dose of azathioprine is appropriate.

Azathioprine is metabolized by xanthine oxidase, and medications that block this enzyme, such as allopurinol, should be avoided since concurrent use can cause azathioprine toxicity.

Plasmapheresis:

In this procedure, blood is removed from the patient, plasma is separated from blood cells and discarded, and blood cells are resuspended in colloid solution and rein infused. Plasmapheresis is effective in treating patients with immune-mediated neuropathies such as those caused by cryoglobulins, SLE, rheumatoid arthritis or polyarteritis nodosa. In addition, individuals with GBS and a large subset of patients with CIDP benefit from this procedure.

The effects of plasma exchange can be summarized as "fast, temporary, and expensive". This procedure does not, by itself, induce permanent remission, and the
ideal application is therefore in acute, self-limited disorders such as GBS. Plasma exchange may also have application in chronic diseases, such as CIDP, where rapid therapeutic effects may occasionally be required.

**Intravenous Immunoglobulin (IVIg):**

IVIg is pooled, human IgG in a form that is safe for intravenous administration. How IVIg affects immunologic function is unknown, but three putative mechanisms have been postulated:

- **Administration of IVIg floods the recipient with an enormously diverse array of antibody molecules, some of which are anti-idiotypic antibodies which may neutralize auto-antibodies in the patient, thereby increasing their clearance and perhaps down-regulating their production.**

- **IVIg inhibits the binding of activated complement to target cells, thus reducing complement-mediated damage to cell membranes.**

- **IVIg infusion is a potent stimulus that down-regulates immunologic production.**

To date, IVIg has been found to be as effective as plasma exchange in treating many immunologic disorders, including Guillain-Barre syndrome and CIDP. IVIg is also reported to be beneficial in treating the polyneuropathy associated with IgG or IgM paraproteins.

**Side effects of IVIg** include fever, myalgia, headache, rash, and occasionally aseptic meningitis and renal failure. The cost of IVIg is equivalent to that of plasma exchange.

**Symptomatic Treatment**

Numerous symptomatic treatments for the pain of peripheral neuropathy are available, and all have their relative risks and benefits.

**Tricyclic Compounds:**

Drugs in this category include amitriptyline, nortriptyline, desipramine, and imipramine. These drugs inhibit the re-uptake of the catecholamine neurotransmitters epinephrine and norepinephrine as well as serotonin, and thus may enhance central pathways that suppress pain transmission. The tricyclic compounds are quite useful for treatment of the burning, dysesthetic pains seen with peripheral neuropathies. Most of these drugs are sedating and, when given at bedtime, promote sleep.

Effective dosages of these drugs for treating chronic neuropathic pain are typically lower than the dosages used for treating depression. We recommend starting with a low single dose at bedtime and slowly increasing the dose over several weeks. Patients should be informed that it may take several weeks before full therapeutic effects are realized.
Anticonvulsants:

Drugs in this category include carbamazepine, phenytoin, gabapentin and lamotrigine. These drugs stabilize neuronal membranes and may thus prevent neuronal "short-circuits" that lead to neuropathic pain. The anticonvulsant drugs are quite useful in treating the lancinating pains frequently seen with trigeminal neuralgia and in some other peripheral neuropathies.

Effective dosages for treating neuropathic pain are similar to the dosages used for treating seizures. Blood levels of these drugs may be monitored and dosages adjusted as needed.

Lamotrigine, a new anti-seizure drug effective for primary generalized seizures, can cause a severe and fatal cutaneous hypersensitivity reaction if the starting dosage is high, and therefore must be started at a very low dose with a very gradual dosage escalation.

Topicals:

Capsaicin, a drug that impedes pain transmission by depleting substance P from sensory nerve fibers, has been found effective in treating refractory neuralgia in several studies. The cream must be applied several times daily to be effective, and patients frequently experience severe burning following each application for one or two weeks following initiation of treatment.

Transdermal lidocaine (Lidoderm), a local anesthetic, also appears to be effective for some patients with neuropathic pain syndromes. This drug is available as an adhesive patch that may be cut to size and replaced every 12 hours.

Surgery

Surgical release of tendons, scar tissue and bony ridges is beneficial in treating many forms of entrapment neuropathy. Nerve transposition may play a role as well in certain clinical circumstances.
REFERENCES


DISORDERS OF NEUROMUSCULAR JUNCTION TRANSMISSION

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Eric L. Logigian, MD  
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Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disorder caused by a humoral and cell-mediated immune response directed against the acetylcholine receptor of skeletal muscle, resulting in weakness and fatiguability of voluntary muscles.

Epidemiology

The prevalence of MG is approximately one per 10,000. This illness is usually sporadic, although 2% to 3% of patients have a positive family history. Other autoimmune diseases such as hypothyroidism, pernicious anemia and rheumatoid arthritis are associated with MG in both patients and their family members, suggesting a genetically determined predisposition to autoimmune dysregulation. MG is seen more frequently in women by a ratio of about 3:2. A bimodal distribution of peak incidence is noted in this disorder, with women having a higher incidence in the third decade and men in the sixth to seventh decade.

Clinical Aspects

Symptoms at onset:

The symptoms of MG usually begin in one of three groups of muscles:

- **Eye:** ptosis and ophthalmoplegia are cardinal symptoms.

- **Bulbar (lower brain stem) musculature:** dysphagia, dysarthria, bifacial paresis, and neck weakness are common.

- **Limb and trunk musculature:** affects proximal muscles usually more than distal ones, and frequently involves the respiratory muscles.

Pathologic fatiguability is a cardinal feature of this disorder. Symptoms of MG are usually more pronounced in the evening. Patients with this disorder also have a relapsing/remitting course.

Numerous factors can cause an exacerbation of symptoms of MG: systemic infections, fever, thyroid disease, pregnancy and the post-partum state, menses, emotional stress, hypokalemia and hypocalcemia, hypermagnesemia, and various medications.

Exacerbations due to identified (or unidentified) causes can result in myasthenic crisis defined by the presence of respiratory embarrassment or by dysphagia and inability to maintain adequate nutrition.
Natural History:

Initial symptoms typically involve extraocular muscles in about 50% of patients, whereas weakness of limb and facial muscles is present in only about 15%, and bulbar muscles in 12%.

Within one month or so, 40% develop generalized symptoms, while 40% of patients have symptoms confined to extraocular muscles, 10% to limb muscles and 10% to bulbar or oculobulbar symptoms.

Ocular myasthenia gravis:

A small subset of patients with MG has purely ocular symptoms. If the disease remains confined to ocular muscles for a year or more, these patients carry a relatively favorable prognosis with only about 10-15% developing more generalized symptoms.

Myasthenia Gravis in Childhood:

MG in childhood can have three distinct forms: transient neonatal MG, congenital MG, and juvenile onset MG. The clinical features of these three forms are detailed in Table 1.

- **Transient neonatal MG** develops in about 12% of infants born to mothers with myasthenia. These infants demonstrate feeding and breathing difficulties as well as generalized weakness shortly after birth due to passive transfer of maternal antibodies. The symptoms are self-limited and usually resolve within several weeks. Treatment is supportive. High maternal antibody titers and the occurrence of neonatal MG in a previous baby are important predictive factors in this form of MG.

- **Congenital MG** is a heterogeneous group of pre- and post-synaptic disorders with diverse etiologies. Symptoms typically begin shortly after birth with respiratory and feeding difficulties and may include prominent extra-ocular weakness. Occasionally symptoms may not begin until the second or third decade. Most forms of congenital MG are inherited in an autosomal recessive pattern and do not appear to be immunologically mediated. The pathologic mechanism differs from patient to patient. Anticholinesterases are the mainstays of therapy for some of the disorders.

- **Juvenile onset MG** appears identical in presentation and pathophysiology with antibody mediated adult onset MG. Acetylcholine receptor antibodies are found in this disorder and anticholinesterase, corticosteroids, thymectomy, and plasma exchange are all effective treatments. Older children, in particular, respond well to thymectomy.
<table>
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<tr>
<td><strong>Age at onset</strong></td>
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<td>First 12 months in most forms</td>
<td>Any age</td>
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<td>AChR-Ab</td>
</tr>
<tr>
<td><strong>Inheritance Pattern</strong></td>
<td>Mother affected</td>
<td>Mainly autosomal recessive</td>
<td>Usually none</td>
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<tr>
<td><strong>Duration of Symptoms</strong></td>
<td>2-4 weeks</td>
<td>Lifelong</td>
<td>Some spontaneous remissions</td>
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<tr>
<td><strong>Symptoms</strong></td>
<td>Feeding and breathing difficulties, generalized weakness</td>
<td>Extraocular weakness, feeding and breathing difficulties</td>
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<tr>
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<td>Anticholinesterase drugs in some forms</td>
<td>Anticholinesterase drugs, corticosteroids, thymectomy, plasma exchange</td>
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</tbody>
</table>
Etiology and Pathogenesis

In order to understand the pathophysiology of MG, the normal function of the neuromuscular junction should be understood.

![Diagram of the neuromuscular junction](image)

Altered humoral immunity:

Acetylcholine, the neurotransmitter at the myoneural junction, is packaged in small vesicles called quanta, in the presynaptic nerve terminals. In response to nerve stimulation, an action potential propagates down the length of the axon, and when it reaches the nerve terminal, large numbers of quanta are released. These quanta diffuse across the synaptic cleft and bind to post-junctional muscle membrane on specialized areas that contain acetylcholine receptors. Binding of acetylcholine results in depolarization of the end plate region. If the end plate potential is above threshold for the adjacent sodium channels in the muscle membrane, the potential is propagated along the muscle fiber, with subsequent muscle contraction. Following binding, the acetylcholine is released, diffuses away from the neuromuscular junction, and is broken down by acetylcholine esterases. It should be noted that during normal neuromuscular transmission, the number of quanta of acetylcholine released in response to nerve stimuli, as well as the number of the resultant acetylcholine-receptor interactions that occur, are in excess of what is necessary to trigger an action potential. This excess provides a safety margin for neuromuscular transmission.
In myasthenia gravis, antibodies to the acetylcholine receptor are found in 87% of patients. These antibodies bind to the receptor, causing receptor blockade and failure in neuromuscular transmission. The antibody-receptor complexes are subsequently internalized by the muscle fiber and broken down by proteolysis, resulting in a significantly reduced number of acetylcholine receptors on the muscle cells. Complement fixation appears to play an important role in this process. The postsynaptic membrane becomes "simplified" due to a reduction in post-junctional folds, and this has been demonstrated with electron microscopy. Thus, in myasthenia gravis, two mechanisms appear to be involved in defective neuromuscular transmission, namely, accelerated degradation of acetylcholine receptors and receptor blockade, both of which reduce the "safety margin" for neuromuscular transmission.

**Altered cellular immunity:**

In addition to the altered humoral immunity noted in patients with MG, altered cellular immunity is also found. The thymus gland, which plays an important role in establishing and maintaining cellular immunity, is abnormal in 75% of patients with MG. Ten percent of patients with the disease have a thymoma. This is seen most commonly in the older myasthenic. Conversely, 44% of patients with thymomas develop MG. Additionally, evidence for thymic hyperplasia has been found in 67% of all patients. Although most thymomas are visible on chest x-ray, chest CT scans are superior for visualizing thymic hyperplasia.

The thymus gland contains a small number of myoid cells that may contain acetylcholine receptors on their surface. It has been postulated that a viral infection of the acetylcholine receptor-containing myoid cells may trigger an immune response against the acetylcholine receptor and result in symptoms of myasthenia.

Other evidence for altered cellular immunity in this disorder includes the fact that myasthenia is associated with certain transplantation antigens. HLA-B8 and DR3 are present in approximately 70% of females with MG who are younger than 40 years of age. HLA-B5 is common in young males, and HLA-A3 is common in older patients with myasthenia.

**Association with other autoimmune diseases:**

As one would expect, given the abnormalities in cellular and humoral immunity, there is an increased association between MG and other autoimmune disorders including thyroid disorders (e.g., hyperthyroidism), systemic lupus erythematosus, rheumatoid arthritis, polymyositis, and pernicious anemia. This association is especially prominent among younger women.
Diagnosis

Both clinical and laboratory features are used to make a diagnosis of MG.

Clinical Examination:

Pathologic Fatigability affecting the eye, bulbar, trunk, or limb musculature is the hallmark for diagnosis. The curtain sign (fatiguable ptosis) is frequently helpful in making the diagnosis. It is quite unusual to see an established case of MG that does not demonstrate any eye abnormalities.

Tensilon (Edrophonium) test:

Edrophonium is an acetylcholine esterase inhibitor which, when injected intravenously, transiently reverses some of the signs of MG. If MG is suspected, a positive effect due to edrophonium should be looked for, and if it is present, the clinical impression of MG may be substantiated.

This test is performed as follows: One or two objectively weak muscles should be identified (levator palpebrae or extraocular muscles) and positive responses agreed upon as an endpoint prior to testing. The patient should be free of all cholinesterase inhibitors at the time of testing. A test dose of 2 mg of edrophonium (0.2 cc) is injected into a freely patent IV and the patient is observed for 30 seconds for adverse effects; an additional 8 mg (0.4 cc) are then injected. A positive response should be evident within 30 to 60 seconds and may persist for one or two minutes. Atropine should be readily available to treat bradyarrhythmias if they develop. Bronchial asthma or cardiac dysrhythmias are relative contraindications to Tensilon testing, and EKG monitoring is advisable in older patients during testing.

Electrophysiological testing:

Both repetitive stimulation studies and single fiber electromyography (EMG) may demonstrate a defect in neuromuscular conduction in patients with MG.

- Repetitive stimulation study: If surface recording electrodes are placed over a muscle belly and the nerve innervating that muscle is electrically stimulated with a supramaximal stimulus, an electrical potential can be recorded whose amplitude is roughly proportional to the number of muscle fibers that are being activated. If there is a progressive failure in neuromuscular transmission, the amplitude of the evoked potential will become progressively smaller with repetitive stimulation. (Figure 2) In MG a decrement of more than 10% in the amplitude of the evoked potentials at stimulating frequencies below 10 Hz is frequently seen in clinically involved muscles. Clinically uninvolved muscles often do not demonstrate this decrement.

If enough muscles are studied (including proximal and facial muscles) repetitive stimulation has a reasonable sensitivity in the range of 85%. In purely ocular disease, the sensitivity is much less. The specificity of the test is reasonably high, but other neuromuscular disorders such as myotonic myopathy, periodic paralysis, and motor neuron disease can occasionally show a significant decrement.
Single Fiber EMG: To understand the concept of single fiber EMG, one must be familiar with the motor unit. To review, the motor unit consists of a single anterior horn cell, its axon and terminal branches, and all the muscle fibers innervated by that anterior horn cell. All muscle fibers innervated by the terminal branches of the same motor unit will be depolarized at about the same time. Because of slight differences in the lengths of the terminal nerve branches, and because of some differences in conduction properties at the neuromuscular junction, the individual muscle fibers of a motor unit are not actually depolarized simultaneously. Taking the action potential from a single muscle fiber as a reference, a similar potential from a muscle fiber in the same motor unit will occur generally within a fraction of a millisecond after the first. In normal muscle, this second potential will always occur when the first is seen. The time interval between the two individual muscle fiber action potentials is slightly variable, and this is known as jitter. (Figure 3). In patients with MG, not only is the jitter increased, but also on occasion, the second potential may disappear entirely, a phenomenon known as blocking. (Figure 3) Increased jitter and blocking in MG occur because of varying degrees of failure at the neuromuscular junction.

Single fiber EMG is a very sensitive test for screening individuals for MG, with up to 95% of myasthenics demonstrating abnormal jitter, including patients with localized ocular myasthenia. This test is time consuming, however, and can also be abnormal in several other neuromuscular disorders including lower motor neuron disease, axonal neuropathies, and some forms of muscular dystrophy.
Figure 15-4
Determination of jitter by simultaneous recording from two muscle fibers, M1 and M2, within the same motor unit. The potential from M1 that triggers the sweep is displayed from the onset with the use of a delay line. The potential from M2 appears after a short interpotential interval determined by the difference in conduction time from the common branching point (B) to the recording electrode (E). The variability of the interpotential interval (jitter) mainly occurs at the motor end-plates, but changes in propagation time along the terminal axons and muscle fibers also contribute. Calibration in the strip recording: 2mV and 500μs. (From Dahlbäck, Ekstedt, and Stålberg, with permission.)

Figure 15-5
Manual calculation of the jitter in a normal (A) and abnormal (B) action potential pair. Five groups of 10 superimpositions are made and ranges of interpotential interval variation are measured for each group. The mean value is then calculated and multiplied by 0.87 to obtain an approximation to Mean Value of Consecutive Difference (calc. MCD), which is comparable to the result determined by a computer (comp. MCD). (From Stålberg and Trenn, with permission.)
Acetylcholine receptor antibody titers:

Elevated titers are seen in approximately 87% of patients with generalized MG. In patients with purely ocular MG, the percentage is somewhat lower (about 50%). There is poor correlation between levels of antibody titers and clinical severity of disease.

Recent evidence suggests that antibody-negative MG may be immunologically and physiologically distinct from the antibody-positive form, and that the serum from these patients contains an antibody that impairs neuromuscular transmission by binding to determinants other than the acetylcholine receptor. Thus, absence of acetylcholine receptor antibodies does not rule out a diagnosis of MG.

Anti-MuSK antibodies have been recently found in a proportion of seronegative generalized MG patients.

Anti-striational (striated muscle) antibodies are present in 85% of myasthenic patients with thymoma, but they are present in only a small percentage of patients without thymoma.

Imaging:

Since approximately 10% of patients with myasthenia gravis have thymoma, most myasthenic patients are imaged with Chest CT or MRI to exclude this tumor. Contrast iodine dye should be avoided, since it can exacerbate MG symptoms.

Differential Diagnosis

NMJ Disorders:

- Lambert Eaton Myasthenic Syndrome (LEMS)
- Botulism
- Anti-cholinesterase toxicity (Cholinergic crisis)
- Organophosphate intoxication
- Congenital myasthenia

Myopathies:

- Oculopharyngeal Muscular Dystrophy
- Mitochondrial myopathy (e.g., progressive external ophthalmoplegia)
- Myotonic Dystrophy
- Dysthyroid myopathy
- Congenital Myopathy (e.g., myotubular congenital myopathy)

Brain Stem or Cranial Nerve Compressive Syndromes

Psychiatric Disorders: (e.g., neurasthenia)
Treatment

Numerous effective treatments are available for MG, and in most cases the disease can be put into complete remission. The appendix details a specific treatment protocol for patients with MG.

Anticholinesterase medications:

Neostigmine and pyridostigmine (Mestinon) are two long-acting anticholinesterases that are available in an oral preparation. Pyridostigmine is slightly longer acting, and in general, peak serum levels with this drug are achieved two hours after oral ingestion. These two agents inhibit the breakdown of acetylcholine by the esterase, permitting it to act longer at the neuromuscular junction. Anticholinesterases merely ameliorate the symptoms of MG and have no effect on the primary pathology. These medications have numerous side effects, including nausea, vomiting, abdominal cramps, diarrhea, and fasciculations that are due to muscarinic (parasympathetic) and nicotinic stimulation.

Injectable forms of neostigmine and pyridostigmine are available for patients unable to swallow the oral form. The parenteral preparations are 10 to 15 times more potent than the oral forms, due to poor oral absorption, and it is imperative that parenteral dosage be adjusted accordingly.

Thymectomy:

Because of numerous thymic abnormalities that have been associated with MG, namely thymic hyperplasia and thymoma, removal of the thymus gland has been advocated as a treatment in this disorder. In fact, about 90% of patients who undergo thymectomy improve, and about 40% of these achieve a clinical remission. The effects of thymectomy are delayed, and frequently they are not evident until several years have elapsed. The benefits of thymectomy appear greater in patients without thymomas who have had the disease for a shorter time.

The best surgical approach for thymectomy is shrouded in controversy. Both the transcervical and transthoracic approaches have their proponents. Since the thymus gland arises from several branchial arches and frequently has ectopic foci, the transthoracic approach affords a much better chance for the removal of the entire gland. Incomplete excision has been associated with the recurrence of myasthenic symptoms.

Perioperative management: performing preoperative and postoperative plasma exchange or IVIg infusion can minimize operative morbidity.

Corticosteroids:

Corticosteroids are the mainstay in treating the immunologic abnormalities associated with MG and are effective in both ocular and generalized forms of the disease. They alter the immune response and presumably reduce the amount of acetylcholine receptor antibodies present in the blood. In addition, they may have a facilitatory role in neuromuscular junction transmission. In contrast to most other oral immunosuppressive agents, they act relatively quickly within days to weeks.
There are few data regarding the effective dose and optimum duration of steroid therapy in MG.

When treatment is begun with high doses of steroids (e.g. 50 mg to 100 mg daily of prednisone), up to 80% of patients experience a transient exacerbation of weakness that at times may be severe. Prednisone should therefore be initiated at a low daily dose (i.e. 20 mg), which is then increased gradually to approximately 1mg/kg per day. This dose should be maintained until clinical improvement plateaus (approximately two to six months), after which a gradual taper is then instituted.

In conjunction with thymectomy and other immunosuppressive therapy (see below), most patients can be tapered down to a relatively low prednisone dose or be tapered off the drug entirely.

Due to significant steroid side effects with daily prednisone therapy, patients should be switched to an alternate-day regimen as soon as possible. Concurrent administration of calcium and Vitamin D or bisphosphonates may help prevent steroid-induced osteoporosis. Periodic eye examinations are recommended to monitor intra-ocular pressure. Treatment with H2 blockers is also recommended to prevent gastritis.

**Immunosuppressive therapy:**

Both azathioprine (Imuran) and cyclosporine (Sandimmune, Neoral) are effective in treating MG unresponsive to anticholinesterases, prednisone, and thymectomy, with a response rate of 80% in one series. A significant number of patients may experience significant hematologic, hepatic, gastrointestinal, infectious, and systemic side effects from these agents necessitating a reduction in dosage or discontinuation of these drugs.

Azathioprine is particularly effective and well-tolerated when used concurrently with steroids in treating myasthenia. In addition to its immunosuppressive actions, it also appears to have a steroid-sparing effect, permitting more rapid and occasionally complete taper of prednisone in many patients. Many elderly patients with myasthenia gravis may be managed on azathioprine monotherapy.

Azathioprine should be initiated at a low dose of 50 mg and slowly increased to approximately 2mg/kg/day, which is given in two or three split doses. Blood counts and liver functions are monitored weekly to monthly, and the dosage is adjusted accordingly. Red blood cell macrocytosis occurs after several months in most patients receiving azathioprine who respond to therapy, and a lack of macrocytosis may indicate suboptimal dosage.

Allopurinol interferes with azathioprine metabolism, and the dose of azathioprine should be lowered considerably in patients receiving allopurinol concurrently. Both azathioprine and cyclophosphamide have a delayed beneficial effect, and several months are typically required before maximal therapeutic benefit is reached.

Cyclosporine, a powerful immunosuppressive agent, has been studied in therapeutic trials in MG. This agent is of theoretical benefit in MG because it appears to inhibit, predominantly, the T lymphocyte-dependent immune response. Preliminary evidence
suggests that cyclosporine, although effective when compared to a placebo, is no more effective than azathioprine or prednisone in the treatment of MG. Furthermore, significant nephrotoxicity requiring discontinuation of the drug occurs in about a third of the patients. Further studies are necessary before cyclosporine can be routinely recommended in the treatment of MG.

Although not yet FDA proved for this indication, mycophenolate mofetil (CellCept) has been recently shown to have promise in the treatment of patients with myasthenia gravis. This agent appears to have a shorter onset of action and possibly fewer side effects than does azathioprine.

**Plasma exchange:**

Plasma exchange (PEx), a process that separates cellular products from plasma in whole blood, reinforcing the former and discarding the latter, has become widely accepted in the treatment of MG. This procedure results in the rapid removal of the humoral factors implicated in the etiology of MG. The therapeutic effects of PEx are relatively transient, and hence, limit the usefulness of this procedure to situations requiring a rapid, short-term therapeutic effect. These include the treatment of myasthenic crises, the improvement of bulbar or respiratory function prior to thymectomy, and the rapid improvement of acute myasthenic symptoms during initiation of immunosuppressive therapy. In addition, occasional patients refractory to all other forms of treatment can be managed with chronic long-interval PEx.

In a review of therapeutic PEx at Strong Memorial Hospital, we found it to be particularly safe and well tolerated in 16 patients with generalized MG who underwent 149 procedures over a two-year period.

**Intravenous Immunoglobulin (IVlg):**

IVlg is pooled, human IgG in a form that is safe for intravenous administration. How IVlg affects immunologic function is unknown, but three putative mechanisms have been postulated:

- Administration of IVlg floods the recipient with an enormously diverse array of antibody molecules, some of which are anti-idiotypic antibodies which may neutralize auto-antibodies in the patient, thereby increasing their clearance and perhaps down-regulating their production.
- IVlg inhibits the binding of activated complement to target cells, thus reducing complement-mediated damage to cell membranes.
- IVlg infusion is a potent stimulus that down-regulates immunologic production.

To date, IVlg has been found to be as effective as plasma exchange in treating many immunologic disorders, including MG.

Side effects of IVlg include fever, myalgia, headache, rash, and occasionally aseptic meningitis and renal failure. The cost of IVlg is equivalent to that of plasma exchange.
Drugs to be used with caution:

Many commonly used drugs have an adverse effect on neuromuscular transmission and should be used with caution in patients with MG. The *aminoglycoside* antibiotics including neomycin, streptomycin, kanamycin, gentamicin, and tobramycin are most frequently implicated, but other antibiotics such as tetracycline, bacitracin and clindamycin can also worsen myasthenic weakness. The *anti-arrhythmics*, including quinine, quinidine, procainamide, propranolol, and phenytoin, and the calcium channel blockers, can also interfere with normal neuromuscular transmission. *Penicillamine* can cause myasthenic-like symptoms, presumably by an antibody-mediated mechanism. *Succinylcholine* and *curare* are contraindicated in patients with MG due to their deleterious effects on neuromuscular junction transmission. *Magnesium* can also affect neuromuscular junction transmission and should be administered very cautiously to patients with known MG.

**LAMBERT EATON MYASTHENIC SYNDROME (LEMS)**

LEMS is a disorder of neuromuscular transmission due to defective acetylcholine release at the presynaptic nerve terminal that results in proximal muscle weakness that improves with repeated effort. LEMS is an autoimmune disorder due to an immunologic response against the pre-synaptic voltage sensitive calcium channel (VSCC) at the motor axon terminal.

**Epidemiology**

LEMS is *more common in males*, by a ratio or 5:1. It is also more frequent in *older individuals*. Up to 70% of patients with this syndrome, particularly men, have a *malignancy* of one kind or another, with *small cell carcinoma of the lung* being the most common. There is also an association between LEMS and other autoimmune diseases, suggesting an *autoimmune etiology*.

**Clinical features**

In contrast to MG, the extraocular and bulbar muscles are *not* as severely involved, but mild ptosis or transient ocular symptoms occur in many patients. *Muscle stretch reflexes* are depressed in this disorder but can be facilitated by vigorous muscle contraction. *Autonomic nervous system involvement* is often seen, resulting in dry mouth, impotence, and even a sluggish pupillary light response.

**Diagnosis**

Electrodiagnostic studies, including *repetitive stimulation studies*, are extremely helpful in making a diagnosis. With high frequency repetitive nerve stimulation, or after brief exercise, LEMS patients show a marked *post-exercise facilitation* or *increment* in the compound muscle action potential amplitude, not typically seen in MG. Approximately 90% of patients have detectable serum antibodies to the VSCC.
Treatment

Treatment of LEMS consists of treating the primary malignancy, if one is present. Corticosteroids, immunosuppressive drugs, as well as PEx and IVlg have been used successfully in some reports.

Guanidine may be effective, by facilitating acetylcholine release at the presynaptic nerve terminal, but this drug has significant side effects that limit its usefulness, including nausea, vomiting, dizziness, hematologic and hepatic toxicity.

3,4-diaminopyridine, another agent that enhances acetylcholine release at the neuromuscular junction, has recently been found effective in treating LEMS in a small number of patients. This drug has fewer side effects than guanidine, but is still not formulated or FDA approved in the US.

Table 2 compares many of the features of LEMS with those of MG.

BOTULISM

Botulism is a disorder of neuromuscular transmission due to blockage of acetylcholine release by botulinum toxin that results in rapidly progressive bulbar dysfunction, visual blurring due to pupillary paralysis, and limb paralysis. The toxin can be acquired from improperly canned food as well as from contaminated wounds, or in infants from colonization of the gut by Clostridium botulinum. Treatment is mainly supportive, including tracheostomy and respiratory support. Botulinum antitoxin may be administered, but serum sickness is a frequent accompaniment to this form of therapy.
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<tr>
<td>Pattern of weakness</td>
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APPENDIX

MYASTHENIA GRAVIS – TREATMENT PROTOCOL

Mild disease:

Pyridostigmine (Mestinon) - start with 15-30 mg po qid and titrate upward daily until symptoms controlled or side effects occur. Usual dose 60-120 mg qid.

Moderate disease:

Add Prednisone - start with 20 mg po qod (every other day) and titrate upward every four days up to a dosage of 2 mg/kg qod. Usual dose 120 mg po qod. Maintain this dosage for several months (usually six months) until the patient plateaus, and then begin a slow prednisone taper (see below).

Severe disease:

The patient should be hospitalized, and steroids are started. Oral prednisone or intravenous methylprednisolone can be used, dependent upon whether the patient can swallow. Start with 20 mg qd and increase every 1-2 days by 20 mg up to a dosage of 1 mg/kg qd. Usual dose 60 mg qd.

Maintain this dosage for 1-2 months and then switch to alternate day prednisone therapy (i.e. change from 60 mg po qd to 120 mg po qod by 20 mg increments/decrements every 2 days as follows: 60 mg - 60 mg - 80 mg - 40 mg - 80 mg - 40 mg - 100 mg - 20 mg - 100 mg - 20 mg - 120 mg - 0 mg - 120 mg - 0 mg.

Prednisone taper:

After a patient has reached a plateau on high-dose steroid therapy, a slow steroid taper is begun, as follows:

<table>
<thead>
<tr>
<th>Month</th>
<th>Prednisone dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 6 (plateau dose)</td>
<td>120 mg po qod</td>
</tr>
<tr>
<td>7</td>
<td>100 mg po qod</td>
</tr>
<tr>
<td>8</td>
<td>80 mg po qod</td>
</tr>
<tr>
<td>10</td>
<td>60 mg po qod</td>
</tr>
<tr>
<td>11</td>
<td>55 mg po qod</td>
</tr>
<tr>
<td>12 - 16</td>
<td>decrease by 5 mg po qod each month</td>
</tr>
<tr>
<td>17 - 28</td>
<td>30 mg po qod</td>
</tr>
<tr>
<td>29</td>
<td>decrease by 2.5 mg po qod every 3 months until a dose of 7.5 - 15 mg po qod is reached, or until symptoms of MG recur</td>
</tr>
</tbody>
</table>

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N.B. Most patients with MG need to take prednisone indefinitely. Discontinuing steroids completely usually results in a recurrence of symptoms of MG.

In patients with significant weakness due to MG, starting high-dose steroids at the outset (without a slow taper upward) frequently produces severe transient worsening of symptoms, and at times this worsening is so severe that the patient requires orotracheal intubation and assisted ventilation. For this reason, patients with generalized MG should be admitted to hospital for initiation of steroid therapy. Starting with a low dose of prednisone and slowly increasing the dosage over 1 - 2 weeks may minimize this transient worsening of MG symptoms.

**Pyridostigmine:**

Pyridostigmine should be maintained as long as the patient is receiving benefit from this drug. Once patients achieve remission due to steroids and immunosuppressives, pyridostigmine should be quickly tapered and discontinued. Continuing pyridostigmine in patients with no active signs of MG only causes side effects.

**Azathioprine:**

Azathioprine is a useful adjunct to prednisone since it is a powerful immunosuppressive agent. It also has a "steroid-sparing" effect, meaning that it allows one to taper prednisone more quickly and sometimes completely. It should therefore be given to older patients who are receiving steroids, and treatment with azathioprine is usually started within several months of starting prednisone. The usual starting dose is 25 - 50 mg po daily, and this is increased every several days until a final dose of 2 - 3 mg/kg daily is reached. Azathioprine is usually given in split-dosage form (2 - 3 times daily).

Blood counts and liver chemistries are monitored weekly for a month, then bi-weekly for two months, then monthly for six - twelve months, then as often as needed, since patients may develop bone marrow suppression and liver toxicity.

Although 2 - 3 mg/kg per day is the optimal dose of azathioprine in most patients, an occasional patient may require a higher dosage. A useful way to determine if higher azathioprine doses are needed is to follow the mean red blood cell volume (MCV). The MCV should show a slight elevation after several months of azathioprine therapy, and a normal MCV may indicate that a higher azathioprine dosage is needed.

It may take up to six months of therapy with azathioprine before a beneficial effect is seen in some patients.

An occasional patient may develop an acute flu-like allergic reaction shortly after azathioprine is started, consisting of fever, nausea, vomiting and systemic symptoms. Liver chemistries are usually elevated. The azathioprine should be promptly discontinued and the patient warned not to take this drug again.

Patients taking azathioprine should be warned not to take allopurinol concurrently with azathioprine, since allopurinol inhibits xanthine oxidase, the enzyme that metabolizes azathioprine. Taking these two drugs together may result in azathioprine toxicity, with nausea, vomiting, elevations in hepatic enzymes, and bone marrow suppression.
Other immunosuppressive drugs:

The use cyclophosphamide or cyclosporine should be reserved for refractory patients with severe disease, since these agents have significant toxic effects.

Plasmapheresis:

A full course of plasmapheresis (five exchanges over a two-week period) should be considered in any patient with severe signs of MG. Plasmapheresis is usually performed when initiating corticosteroids. When performed in this setting, significant clinical improvement may be seen within two weeks of initiating this procedure. In addition, a short course of plasmapheresis is helpful when preparing a patient for thymectomy.

Thymectomy:

Thymectomy should be performed in any young patient with generalized MG. In general, we perform thymectomies within 1-2 years of diagnosis. The trans-sternal approach is utilized, since this approach allows removal of most thymic tissue. Although we have no specific upper age limit for thymectomy, we rarely perform this procedure in elderly patients who have no evidence for thymoma.

We prepare patients for thymectomy by discontinuing all anticholinesterases prior to surgery, and performing a short course of plasmapheresis (2-3 exchanges). Discontinuing anticholinesterases prior to surgery reduces the amount of post-operative oral secretions that may interfere with early extubation. Plasmapheresis prior to surgery insures adequate respiratory and pharyngeal muscle function post-extubation.

Intravenous Immunoglobulin (IVIg):

A two-day course of IVIg (1mg/kg/d) may be as effective as a full course of plasmapheresis in patients with severe signs of MG.

Adjuvant measures:

Ephedrine and KCl may make patients with MG feel stronger. Both of these medications may be taken 3-4 times daily. Many of our patients on every-other-day prednisone therapy take both ephedrine and KCl on their "off-days" of prednisone to give them extra energy.
REFERENCES


