Introduction to Disorders of the Motor Unit “Plus”

Motor Neuron Disease

Motor neuron disease refers to a diverse group of disorders where only upper motor neurons, lower motor neurons, or both are affected. Upper motor neurons comprise the corticospinal tract and the corticobulbar tract, controlling the anterior horn cells and cranial nerve motor nuclei (collectively the lower motor neurons), respectively. "Bulb" refers to the lower brain stem, which is the location of the cranial nerve motor nuclei that innervate muscles of the jaws, face, palate, pharynx, larynx, and tongue. The severity and prognosis vary widely amongst the degenerative motor neuron diseases discussed here. In other instances, motor neurons can also be destroyed by rare immune-mediated disorders or viruses like polio.

Spinal muscular atrophy (or Hereditary motor neuropathies) is the term for a group of disorders involving just anterior horn cells. Many are hereditary in nature. The clinical findings consist of the lower motor neuron signs of weakness, atrophy, fasciculations, and loss of reflexes. Werdnig Hoffman disease is an infantile onset spinal muscular atrophy with fatal outcome due to respiratory weakness. Less common types of spinal muscular atrophy become symptomatic in childhood or adult life, creating nonfatal disabilities. Benign focal amyotrophy manifests in adults as a slowly progressive atrophy of one limb or restricted segments of limbs, with a normal life span.

Primary lateral sclerosis describes the familial degeneration of the corticospinal tract in lateral columns of the spinal cord, not due to structural (spinal stenosis from degenerative arthritis) or metabolic (vitamin B-12 deficiency) lesions. Weakness is accompanied by the upper motor neuron signs of spasticity, hyperreflexia, and Babinski signs.

Pseudobulbar palsy encompasses several disorders where only the corticobulbar tract is involved, causing facial weakness, impaired chewing, dysarthria, dysphagia, and hoarseness. The jaw jerk is typically increased, while fasciculations and atrophy are absent despite significant weakness. Pseudobulbar palsy may be caused by bilateral, multiple cerebral infarctions, brain tumors, lesions of multiple sclerosis, or brain trauma. Rarely is it from a degenerative disorder. It should be noted that the diagnosis of any of these motor neuron diseases is made with more certainty over a long period of observation, since amyotrophic lateral sclerosis may begin with only upper or lower motor neuron signs and symptoms in one part of the body.

Unfortunately, the most common motor neuron disease, amyotrophic lateral sclerosis (ALS at times still referred to as Lou Gehrig disease), is the most severe. It begins at 40 to 70 years of age with men outnumbering women. Initially there may be focal weakness and atrophy in a limb, such as a shoulder or leg (foot drop), which subsequently spreads and becomes bilateral. Other patients may first have dysarthria, hoarseness, or impaired swallowing (bulbar ALS).

Both upper and lower motor neurons degenerate, with clinical signs of each, including typically widespread fasciculations. Spasticity and hyperreflexia accompany severe atrophy and weakness. Patients die within months to a few years from respiratory failure or complications such as infection. The extraocular muscles and sphincters of bladder and bowel are spared. Rarely ALS is familial, where free radical toxicity destroys motor neurons because of a defective superoxide dismutase enzyme. In the more common sporadic type of ALS, the cause is unknown.

Pathological findings are degeneration of corticospinal and corticobulbar tracts, gliosis and loss of anterior horn cells and pyramidal neurons, and neurogenic atrophy of muscle. The clinical diagnosis is often challenging early in its course, when obvious upper and lower motor neuron signs may not be fully apparent. A cervical radiculomyelopathy from degenerative disc disease may mimic ALS by causing lower motor neuron signs in the upper limbs and upper motor neuron signs in the lower limbs. Other ALS mimics include stroke and rare auto-immune neuromuscular disorders. If a patient has only bulbar symptoms or symptoms restricted to one limb, EDX may help by demonstrating subclinical denervation or reinnervation in many other muscles, as well as excluding neuropathy or myopathy.

Sadly there is no curative treatment for ALS. Survival is prolonged a few months by taking riluzole®, the only drug showing a limited benefit in a controlled trial. The excitotoxic effect of glutamate at the NMDA (N-methyl-D-aspartate) receptors of motor neurons is opposed by riluzole®. Recently an i.v. administered medication, edaravone®, has been used for ALS and acts as a free radical scavenger, but its long-term effectiveness is yet to be clarified. As ALS weakness progresses, patients and families must make choices about mechanical means of ventilation and nutrition.
Neuropathy

Types of neuropathy
"Neuropathy" is a broad, generic term which refers to a variety of syndromes in which one or more nerves are affected by any of several known or unknown causes. Mononeuropathy refers to involvement of a single major, named nerve usually by trauma or compression. The associated sensory and motor deficits reflect the anatomic distribution of the nerve. Localization can be done from the bedside neurological examination and further refined by electromyography (EMG). Polyneuropathy (or peripheral neuropathy) is a disorder of multiple nerves, both major and small, unnamed nerves, or branches.

In the most common polyneuropathies, symptoms and signs are symmetrical and sensory loss or impairment occurs early and often remains prominent. Numbness and tingling, sometimes to an annoying or painful degree, usually begins distally in the toes and feet, later affecting the fingers and hands. (The longest nerves in the body may be affected first since their metabolic maintenance and axoplasmic flow are more susceptible to neurotoxic factors.) These complaints and the sensory deficits found on examination are in a "stocking and glove" pattern (Figure 1).

Patients may also describe paresthesia, a spontaneous tingling, "pins and needles" sensation, or dysesthesia, an unpleasant sensation from a non-noxious stimulus. Any weakness and muscle atrophy also begin or predominates in the distal limbs. There is early loss or decrease of reflexes. Other symptoms occur if autonomic nerves are involved, including orthostatic hypotension, incontinence, impotence, or sweating abnormalities.

Pathology of neuropathy
Demyelination and axonal degeneration are the two basic pathological processes in neuropathy. One or the other tends to predominate or occur initially. Demyelination (Figure 2A and B) characterizes a mononeuropathy from focal compression, such as carpal tunnel syndrome, where the median nerve is compressed at the wrist. Demyelination is also the primary process in most cases of Guillain-Barré syndrome, an acute type of polyneuropathy. In either case, if the neuropathy progresses over time or is initially severe, axonal degeneration may also occur, with less chance for recovery. If there is mild focal trauma to a nerve, recovery may occur sooner and more completely once any swelling has resolved or any remyelination of intact axons has occurred.

With a more severe crush or penetrating focal nerve injury, axonal loss occurs via Wallerian degeneration (Figure 2C). Here, axons and myelin degenerate distal to the point of nerve injury. Recovery takes longer and may be incomplete, depending on whether any remaining perineurium can "guide" regrowing or sprouting axons to their intended targets. Without such "support scaffolding" of perineurium, resprouting axons pile up in a bulbous neuroma, which is often painful. Most polyneuropathies from toxic-metabolic causes have axonal degeneration (Figure 2D) as the primary pathology, with demyelination as a secondary or additional process.
Diagnosis and treatment of polyneuropathy

The clinical pattern of nerve involvement is one clue about the underlying cause. Most mononeuropathies are due to trauma, usually evident from the history, or occur at typical sites of nerve compression or entrapment, such as the median nerve at the wrist, the ulnar nerve at the elbow, and the common peroneal nerve at the fibular head. A **multiple mononeuropathy syndrome** may be due to a systemic illness which is inflammatory or autoimmune (lupus erythematosus), infiltrative (sarcoidosis), or infectious (leprosy). Finding the cause of some non-acute polyneuropathies is a challenge, with an unknown etiology in approximately 50% to 60% of patients despite thorough evaluation.

Other elements of the patient's history suggest clues for the etiology of a non-acute polyneuropathy. A polyneuropathy may have been caused by current or recent medications, such as chemotherapy. Toxic neuropathies are due to exposure to neurotoxins at the workplace, such as organic solvents, or from social habits, such as alcoholism. Malnutrition and vitamin deficiencies may also cause a polyneuropathy. A positive family history of similar symptoms raises the possibility of a hereditary neuropathy, which often begins early in life. If limb weakness occurs early during growth and development, *pes cavus* (high-arched feet), hammertoes, or scoliosis may occur. Other affected family members may be unaware of these findings, so examining all available family members is sometimes helpful if a hereditary neuropathy is suspected.

Further diagnostic help may be obtained from an **electrodiagnostic study (EDX)**, which tests the electrical activity and function of nerves and muscles. EDX may help clarify any subtle neuropathic clinical signs with regards to a more precise localization of the lesion and its severity. It may detect abnormalities not found on the clinical examination and helps distinguish a neuropathy from a radiculopathy or from a myopathy in confusing cases. When the clinical picture or EDX suggest a chronic polyneuropathy is due to inflammatory, immune-mediated, or vasculitic causes, a sural (sensory nerve) biopsy helps confirm the diagnosis. Typically, the sural nerve in the foot is biopsied which leaves permanent numbness along the lateral foot. Motor nerves are not biopsied since that would create a permanent motor deficit, but biopsy of an adjacent muscle may reveal pathological changes indicative of motor nerve denervation.

If a non-acute polyneuropathy has no helpful historical clues as to its etiology and the EMG test is nonspecific, "screening" for a cause, particularly a treatable one, is done with blood tests for diabetes, liver or renal dysfunction, vitamin B12 deficiency, and hypothyroidism. A complete blood count helps screen for anemia or other blood disorders like leukemia.

Treatment of the neuropathy depends on the underlying cause, if one is found. A significant median mononeuropathy at the wrist (from entrapment in the carpal tunnel) may benefit from surgical decompression. Optimal glycemic control may help improve diabetic polyneuropathy. Chronic weakness of the distal limbs may require braces, splints, or use of a cane or walker. Ankle-foot orthoses (AFOs) prevent tripping in the setting of foot drop. Whether or not a direct cause of polyneuropathy is found, many patients suffer from constant neuropathic pain in their feet. Topical capsaicin, a substance P depleter, or lidocaine patches can be applied over the involved skin. Effective oral medications for neuropathic pain include anticonvulsants (gabapentin, pregabalin, carbamazepine) and antidepressants (duloxetine, amitriptyline) which all interact with neurotransmitters.

**Clinical polyneuropathy syndromes**

One of the most rapidly progressive polyneuropathies is the **Guillain-Barré syndrome**. It affects patients of all ages, most often following a recent viral illness, but also after surgery or trauma. Here the immune system targets peripheral nerve myelin, which was possibly modified by or antigenically resembles the virus encountered weeks earlier. The typical clinical picture is that of an ascending, reflexive paralysis, where the lower limbs are affected first. Within only hours to days, the weakness may spread to involve the trunk, upper limbs, respiratory muscles, face, bulbar, and even extraocular muscles. Although patients may complain of tingling or numbness, signs of sensory impairment are minimal. The progression of weakness plateaus after 3-4 weeks’ time. These patients require hospitalization, including observation in an intensive care unit, since mechanical ventilation may be needed.

An EDX test usually shows evidence of asymmetrical demyelination in proximal and distal segments of various nerves. An elevated cerebrospinal fluid (CSF) protein may be detected with few if any white blood cells and no signs of infection (**albumino-cytologic dissociation**). Despite even severe weakness, most patients recover fully, while a minority survives with some residual neurological deficits. Recovery may be hastened by treatment with
plasmapheresis, where physical removal of circulating antibodies lessens the autoimmune attack on peripheral nerve myelin, or with infusion of intravenous gamma globulin, which provides high doses of antibodies which counteract, block or down-regulate the autoimmune process.

Most polyneuropathies are chronic and develop over months to years. One of the most frequent etiologies is diabetes mellitus, which may also cause isolated or multiple mononeuropathies, autonomic neuropathies (diabetic gastroparesis or orthostatic hypotension), and cranial neuropathies (diabetic third nerve palsy). Other etiologies include metabolic or endocrine disorders (uremia, hypothyroidism), rheumatologic disease (rheumatoid arthritis, systemic lupus erythematosus), cancer or myeloma (sometimes associated with an antibody directed against peripheral nerve), infection (ADS, leprosy (the latter more common outside the U.S.)), nutritional deficiencies (B vitamins), and toxins (alcohol, lead, solvents, drugs).

Neuromuscular Junction Disorders

The Neuromuscular Junction (NMJ)

Muscle contraction occurs when lower motor neurons are depolarized, and propagating action potentials are generated that descend the axon to the muscle fibers they innervate. This terminal axon/muscle fiber interface is referred to as the neuromuscular junction (NMJ), each muscle fiber has only one NMJ and the axonal component is referred to as presynaptic and the adjacent muscle membrane (sarcolemma) is referred to as postsynaptic (Figure 3).

When those action potentials reach those motor neuron terminals (presynaptic), calcium influx occurs and facilitates release of acetylcholine (ACh) from vesicles within those terminals. The ACh is release into the synaptic cleft (space between the pre- and postsynaptic membranes of the NMJ) and binds to specific nicotinic acetylcholine receptors (AChR) on the postsynaptic muscle membrane, activating ion channels and creating an end plate potential (EPP). If enough EPPs simultaneously occur, it generates a self-propagating muscle fiber membrane depolarization that descends along the muscle membrane in either direction.

Normally, the EPPs far exceed the threshold required to initiating this self-propagating muscle embrace potential. As the wave of depolarization travels down the muscle membrane it spreads into the muscle fiber through the T tubules. These T tubules abut against the muscle fiber sarcoplasmic reticulum and resulting in its release of calcium that initiates the interaction of actin and myosin within the muscle fiber and resulting in muscle fiber contraction.

This effect of ACh and the EPP it generates are limited by synaptic acetylcholinesterase (AChE), which breaks down ACh. During repetitive muscle contractions or exercise, lesser amounts of ACh are released from motor neuron terminals by subsequent action potentials. Although the EPP amplitudes are thereby decreased, they remain above the threshold for generating muscle fiber action potentials, and adequate muscle contraction is still achieved. This is the “safety factor” at normal neuromuscular junctions. In myasthenia gravis, in which many AChRs are degraded or blocked (Figure 3), less ACh can bind, producing EPPs which are below the threshold for generating muscle fiber action potential and hence contraction. Clinically weakness then occurs at rest or after repeated activity or exercise. Myasthenic weakness can be improved by drugs that inhibit AChE, effectively “increasing” the amplitude and duration of the EPP and allowing muscle contraction to occur.
Myasthenia gravis (MG) is an autoimmune disorder of the postsynaptic NMJ. Although less common than MG, two other NMJ disorders worth mentioning involve the presynaptic NMJ, where the release of ACh is impaired. Lambert-Eaton Myasthenic Syndrome (LEMS) is also an autoimmune disease, but the target is the voltage-gated calcium channel at the presynaptic membrane, not the AChR. In botulism a bacterial toxin binds presynaptically at the NMJ, preventing ACh release and causing weakness. (Congenital myasthenia refers to heterogeneous disorders in which the safety margin of neuromuscular transmission is compromised by one or more specific mechanisms. The diseased proteins reside in the nerve terminal, the synaptic basal lamina, or in the postsynaptic region, or at multiple sites at the neuromuscular junction as well as in other tissues.)

Myasthenia Gravis (MG)

The immune system and MG

Myasthenia gravis is an autoimmune disease, where the otherwise normally functioning immune system inappropriately reacts to a specific, normal self-antigen. With the help of T-cells, B-cells produce antibodies which block and destroy AChRs faster than new AChRs can be synthesized. The normal architecture and folding of the postsynaptic NMJ is lost when viewed under electron microscopy. The thymus gland, critical for T-cell development, appears to be an important factor in the etiology of MG. In most myasthenic patients, abnormalities of the thymus occur, consisting more commonly of glandular enlargement or hyperplasia, and less commonly of a thymic tumor or thymoma. The thymus may be where myasthenic autoimmunity begins, but the actual triggers or inciting events are unknown.

Clinical features of MG

Autoimmune myasthenia gravis can begin at any age, from childhood to late adult life, with a prevalence of 20 people per 100,000. As a neuromuscular junction disorder, it causes only motor symptoms manifest as weakness and fatigue of skeletal muscles, without pain, sensory or cognitive impairment. Fatigue here refers to muscular weakness encountered during non-strenuous activity, such as chewing a meal, climbing a flight of stairs, having a conversation, or watching a movie. Fatigue does not refer to lack of sleep, exhaustion or feeling "tired all over."

The most common initial symptoms include ptosis (eyelid drooping), diplopia (double vision from asymmetrically weak extraocular muscles), dysarthria (slurred speech), and dysphagia (weakness of swallowing). These may be present on awakening and remain constant throughout the day in some patients. Others will feel fine in the morning after a night’s rest, but develop symptoms later in the day, especially after sustained activity or exertion. For example, dysarthria may occur only after a long conversation, or diplopia may occur after reading for an hour; both may improve or resolve after a period of rest. Some patients have milder or more localized symptoms which only slowly become troublesome, while others may have more severe, fulminant weakness that involves most of the body. Asymmetrical weakness is common, with more droopiness of one eyelid, or more "crookedness" of one eye. When attempting to smile, a horizontal snarl may result, or the face may sag (Figure 4). One or more limbs can likewise weaken, while respiratory weakness or choking are ominous signs.

The severity or extent of weakness and fatigue may vary from hour to hour or day to day. On examination, sensation, muscle stretch reflexes, cognition, and higher cortical functions remain normal, with muscle atrophy developing only rarely in severe MG of long duration. Although many myasthenic patients have initial symptoms of only ptosis or diplopia, only a minority of them, about 10-20%, will continue to have only these visual symptoms after 2 to 3 years’ time. This is ocular myasthenia, a restricted form of MG. Most MG patients, about 80-90%, eventually develop generalized myasthenia gravis, having more than just visual or ocular symptoms. In neonatal myasthenia, healthy newborns of myasthenic mothers may have MG symptoms for a few days, until maternal antibodies "wash out" of their system.

Figure 4. Despite contraction of forehead muscles, the eyelids still droop (ptosis). An open-mouthed snarl demonstrates facial weakness when smiling.
In myasthenic crisis, profound weakness may cause quadriplegia, with the patient unable to speak, swallow or breathe. Myasthenic crisis may be suddenly triggered by a serious infection or other systemic illness in a myasthenic patient, or may unpredictably develop over days in someone with severe MG. It is a neurological emergency often requiring intubation and mechanical ventilation, intensive care in the hospital, treatment of any concurrent infection and acute, aggressive treatment of MG itself.

It should be noted that a few other neurological conditions besides myasthenic crisis cause acute paralysis of speech, chewing, swallowing, limb and respiratory muscles. All these patients need emergent intensive care and ventilatory support, often before the specific cause is identified. The differential diagnosis includes an extensive infarction of the brain stem, where hyperreflexia may be noted, and the lesion confirmed by MRI scan. Guillain-Barre syndrome usually evolves over a few days, with areflexia and sensory impairment accompanying the weakness, the diagnosis confirmed by electromyography (EDX) and an elevated cerebrospinal fluid protein. Acute paralysis from a spinal cord lesion spares the cranial nerves and has a localizing level of sensory loss, sometimes with neck or back pain. Spinal cord MRI reveals any causative tumor or inflammation (multiple sclerosis, viral myelitis), which may begin to improve with intravenous corticosteroids. In myasthenic crisis, sensation and reflexes remain normal.

**Diagnosis of MG**

The clinical history should be very suggestive or typical of MG, since the examination of a rested patient early in the day may be neurologically normal. If a truly objective sign of weakness is present, such as ptosis, marked improvement after injection of an acetylcholinesterase inhibitor drug like edrophonium (Tensilon®) strongly suggests MG. In the electromyography laboratory, myasthenic patients undergoing repetitive nerve stimulation or single fiber jitter analysis may show NMJ abnormalities typical of MG. The most specific diagnostic test for MG is the presence of serum AChR antibodies. These are detected in 80-90% of patients with generalized MG, but only in about half of those with the restricted form of ocular MG. Some of the 10-20% of seronegative patients with generalized MG have been found to have serum antibodies to MuSK (muscle specific receptor tyrosine kinase), an NMJ protein important for the clustering of AChRs.

**Treatment of autoimmune MG**

Historically, weak myasthenic patients appeared like those poisoned by curare, an NMJ antagonist, and their muscles would weaken when given very small amounts of curare which had no effect on normal individuals. This led in 1934 to the first successful use of a cholinesterase inhibitor in treating MG by Mary Walker, a London medical resident. Today, oral anticholinesterase drugs, most commonly pyridostigmine (Mestinon®), are the first treatment of MG. Dose escalation must be monitored closely since high doses may produce a cholinergic crisis, consisting of weakness, sweatiness, salivation, diarrhea, and excessive urination. Anticholinesterase drugs may be the only treatment needed in some patients, whereas others require the addition of immunosuppressant drugs. Some patients go into remission, whether spontaneously or after treatment, and their symptoms gradually disappear.

In 1939, Blalock removed a thymoma, previously irradiated, from a myasthenic woman who struggled through several myasthenic crises, only to slowly improve postoperatively and achieve remission years later. From then on, thymectomy was often performed in younger myasthenics without thymoma, benefitting some patients. A controlled, randomized trial of thymectomy for MG remains to be completed, however.

Various immunosuppressant drugs are also used to treat MG, unfortunately not selectively inhibiting production of AChR antibodies, but suppressing the immune system. These include corticosteroids, especially prednisone, and drugs commonly given to organ transplant patients, like azathioprine, mycophenolate, and cyclosporine. In the setting of myasthenic crisis, where severe weakness is life-threatening and rapidly effective treatment is needed, intravenous immunoglobulin (IVIG) or plasmapheresis are used. The gamma globulin component of plasma, containing all circulating antibodies as well as anti-AChR, is physically removed by a plasmapheresis machine through which a patient’s blood is pumped. This removal of circulating anti-AChR temporarily improves MG symptoms. The exact mechanism by which IVIG helps MG is less clear but may involve down-regulation of the immune system triggered by high levels of infused circulating antibodies, or infusion of unknown antibodies which attack or block the action of anti-AChR. IVIG also has a temporary therapeutic benefit.
Lambert-Eaton Myasthenic Syndrome (LEMS)

Clinical features of LEMS
As another NMJ disorder, muscle fatigue and weakness occur in LEMS, but tend to affect the proximal muscles of the shoulders and hips as well as the trunk, mimicking the weakness also seen in a myopathy. Symptoms do not usually involve the eyes, swallowing, or speech. Muscle stretch reflexes may appear decreased but reappear along with improved strength after a brief period of isometric exercise, which can be tested during the bedside examination. LEMS also differs from MG in that autonomic symptoms may occur, such as dry mouth, orthostatic hypotension, or erectile dysfunction. In 50-60% of LEMS patients, the autoimmune dysfunction is related to an underlying cancer (paraneoplastic), most often small cell carcinoma of the lung (SCLC), while in the remainder an autoimmune trigger elicited by an underlying autoimmune disease. Again, sensory deficits, cognitive symptoms, and pain are not usually found in LEMS.

Diagnosis and treatment of LEMS
Repetitive nerve stimulation and other tests in the electromyography laboratory usually show presynaptic NMJ abnormalities typical of LEMS. In many patients a serum antibody to the voltage-gated calcium channel is found. A thorough search for a small cell carcinoma of the lung is needed, as this cancer may be only present as a tiny endobronchial lesion. If detected, treatment is primarily directed towards the underlying cancer. Strength and fatigue may improve with drugs that enhance the release of ACh, such as guanidine or 3,4-diaminopyridine. Immunosuppressant drugs and plasmapheresis benefit those patients where LEMS is caused by an underlying autoimmune disorder. However, the treatment of LEMS is generally not as effective as that for MG.

Myopathy

Diagnosis and treatment of myopathy
Myopathies are several diseases of various causes where the primary pathology affects muscle directly. In contrast to the typical distal limb weakness and early loss of reflexes in polyneuropathy, most myopathies have proximal weakness or fatigue, normal sensation, and late loss of reflexes only after significant atrophy has occurred. Pain is usually not prominent but may occur with muscle cramps or spasms during physical activity.

How rapidly weakness occurs, and other historical clues help make a specific diagnosis. A patient with a severe influenza infection may rapidly weaken from viral induced breakdown of muscle fibers, the byproducts of which may precipitate in renal tubules, leading to kidney failure (myoglobinuria from rhabdomyolysis). Various medications may adversely affect muscle over periods of weeks to months, such as statin drugs given to patients with high cholesterol levels or patients on corticosteroids for rheumatological diseases. Endocrine disorders like Cushing's disease and hypothyroidism can cause myopathy. Muscle pain or weakness developing primarily during exercise may signal a hereditary condition involving glycogen or lipid metabolism in muscle. Some of the more chronically developing myopathies may also be hereditary in nature, where a detailed family history is crucial, followed by examination of other affected relatives.

The diagnostic testing in myopathy supplements any historical findings and physical signs and includes measurement of serum creatine kinase (CK), a muscle enzyme often nonspecifically elevated in diseases of muscle. EMG testing helps to confirm the diagnosis and rules out other causes of weakness from neuropathy, myasthenia, or motor neuron disease. In selected patients a muscle biopsy is performed for a pathological diagnosis.

Clinical myopathy syndromes
"Polymyositis" literally means inflammation of multiple muscles and may be due to infections or drug reactions. In the United States, polymyositis more commonly refers to an autoimmune disorder affecting muscle, usually in adulthood. The proximal weakness evolves over weeks to months, affecting patients to different degrees. There may be difficulty climbing stairs, arising from a chair, holding up the head, or raising the arms. A rash involving the periorbital areas and knuckles is typical of dermatomyositis, where both skin and muscle are involved. Some myositis patients have or subsequently develop a systemic rheumatological disorder, and rarely there is an underlying cancer,
especially small cell lung carcinoma. EDX testing helps support the clinical diagnosis. Typical muscle biopsy findings show inflammatory cell infiltrates amidst necrotic and regenerating muscle fibers. Most patients improve with oral corticosteroids or other immunosuppressant medication.

**Muscular dystrophies** are hereditary myopathies of variable progression and severity. In some types, patients may be mildly affected or asymptomatic by adulthood, while children or teenagers may die from the more severe muscular dystrophies. An example of the latter is **Duchenne** (X-linked) **muscular dystrophy** which involves virtually total deficiency of muscle dystrophin, an important structural protein. Affected young boys begin having more trouble running, climbing or walking. The examiner may observe the **Gower’s maneuver** as the child attempts to get up off the floor using his upper limbs to compensate for weak trunk and pelvic muscles (Figure 5). The calf muscles appear to be unusually enlarged (**pseudohypertrophy**) as muscle is replaced by fat and connective tissue. Death occurs after weakening of the respiratory muscles or from the associated cardiomyopathy.

Other types of muscular dystrophy are less severe and may primarily affect a few muscles, such as **facioscapulohumeral** or **oculopharyngeal dystrophy**. Abnormalities of different muscle membrane proteins or glycoproteins characterize certain other muscular dystrophies.

Other hereditary myopathies have a pathogenesis which affects other body organs. **Myotonic dystrophy type I** is due to excessive trinucleotide DNA repeats on chromosome 19, producing an abnormal protein kinase in muscle fibers. It is an autosomal dominant disorder. Weakness affects the distal limbs as well as the neck, face and jaws. The mouth often hangs open due to weak jaw closure. **Myotonia** is the peculiar impaired relaxation of muscle after volitional contraction. Patients may complain of difficulty letting go of a handshake or doorknob. Percussion of the thenar muscles with a reflex hammer also elicits myotonia on the clinical examination. While some medications may lessen the myotonia, nothing improves the weakness.

The trinucleotide abnormality adversely affects gene function in other organs, causing other somatic features in myotonic dystrophy type I patients, such as cataracts, frontal baldness, infertility, and cardiac arrhythmias. Although no curative treatment currently exists, a cardiac pacemaker may be life-preserving in patients with heart block. Mitochondrial myopathies are hereditary disorders with abnormalities of various mitochondrial enzymes, often affecting the brain in addition to muscle.
Clinical Localization of the site of Weakness

Overview of physical signs in conditions associated with weakness

<table>
<thead>
<tr>
<th>Sign</th>
<th>Upper motor neuron</th>
<th>Lower motor neuron</th>
<th>Primary muscle disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wasting</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Fasciculations</td>
<td>Present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distribution of weakness</td>
<td>Hemiplegic</td>
<td>Usually paraplegic or quadriplegic</td>
<td>In distribution of individual nerve or root; Usually distal in a polyneuropathy</td>
</tr>
<tr>
<td>Tone</td>
<td>Spastic</td>
<td>Spastic</td>
<td>Normal</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Brisk</td>
<td>Brisk</td>
<td>Depressed</td>
</tr>
<tr>
<td>Babinski sign</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Sensory loss</td>
<td>Usually present</td>
<td>Usually present</td>
<td>Usually distal extremities in a polyneuropathy</td>
</tr>
</tbody>
</table>

Approach to a Diagnosis begins with the History and Physical ...

- History of Present illness
  - Mode of onset, Course, Associated Symptoms, Severity of symptoms
- Medical History
- Developmental History
- Family History
- Examination
  - Muscle appearance, Muscle tone, Muscle power, Muscle stretch reflexes
  - Sensory examination
  - Coordination
  - Gait

... and then a Clinical Localization is considered

- **Upper Motor Neuron Lesion**
  - **GENERAL SIGNS**
    - Pattern of weakness or paralysis
    - Minimal muscle wasting
    - Spasticity in the involved limbs
    - Increased or brisk muscle stretch reflexes and an extensor toe sign (e.g. Babinski sign)
    - A pattern of sensory loss
  - **LOCALIZATION OF THE SITE OF THE UNDERLYING LESION**
    - Parasagittal
    - Discrete lesion of the cerebral cortex
    - Lesion in the internal capsule
    - Brainstem lesion
    - Spinal cord lesion
• **Lower Motor Neuron Lesion**
  o **GENERAL SIGNS**
    ▪ Weakness or paralysis
    ▪ Wasting and fasciculations of involved muscles
    ▪ Hypotonia or flaccidity
    ▪ Decrease in muscle stretch reflexes
    ▪ Absent extensor toe sign (Babinski sign)
  o **LOCALIZATION OF THE SITE OF THE UNDERLYING LESION**
    ▪ **Anterior horn cell**
      ▪ **Key symptoms**: Weakness and wasting of muscles, can be associated with dysarthria or dysphagia, absence of sensory symptoms
      ▪ **Key signs**: Weakness, wasting and often fasciculations in affected muscles. Weakness and fasciculations may be noted in cranial nerve innervated muscles, hypo- or areflexia of involved muscles, absence of sensory abnormalities
    ▪ **Root**
      ▪ **Key symptoms**: Radicular or root pain; described as sharp or lancinating and referred to a specific dermatome. Often worsens with specific maneuvers (increased intraspinal pressure or stretching of the nerve root) and sensory symptoms are in the same dermatome. Weakness of muscles of that involved myotome (e.g. root)
      ▪ **Key signs**: Hypesthesis or anesthesia in the specific dermatome, but may be minimal because of overlap of cutaneous supply; accentuate pain with specific maneuvers. Weakness, atrophy (and at times fasciculations) in affected muscles, hypo- or areflexia of involved root
    ▪ **Plexus**
      ▪ **Key symptoms**: Pain that is described as aching and involving either what appears to be a "root" or nerve distribution. Weakness of muscles of that involved plexus, sensory symptoms may or may not be present and dependent on the division(s) of the plexus involved
      ▪ **Key signs**: Hypesthesis or anesthesia that is outside a single dermatome or nerve distribution. Weakness, wasting and at times fasciculations in affected muscles that are outside an individual nerve root or nerve distribution, hypo- or areflexia may be present
    ▪ **Nerve**
      ▪ **Key symptoms**: Pain and sensory loss within the distribution of a single nerve. Weakness of those muscles innervated by a specific nerve
      ▪ **Key signs**: Hypesthesis or anesthesia that is within the distribution of a specific nerve. Weakness, wasting (fasciculations can occur, but are uncommon) in the affected muscles innervated by that same individual nerve, hypo- or areflexia is unusual
  ▪ **Polyneuropathy**
    ▪ **Key symptoms**: Typically, distal numbness and weakness (legs worse and worse distally); burning dysesthetic pain, worse at night, autonomic dysfunction. Distal weakness and atrophy. Gait instability
    ▪ **Key signs**: Typically, a “Stocking and glove” pattern of sensory loss. Distal weakness and wasting, absent or diminished reflexes, associated foot deformities

• **Neuromuscular Junction**
  o **GENERAL SIGNS**
    ▪ Weakness or paralysis that is variable in severity or worsened with activity
    ▪ Normal or reduced muscle tone
    ▪ Normal or depressed muscle stretch reflexes
    ▪ Absent extensor toe sign (Babinski sign)
    ▪ No sensory changes

• **Myopathic Disorders**
  o **GENERAL SIGNS**
    ▪ Weakness or paralysis that is often worse proximally
    ▪ Muscle wasting in late stages of the disease
    ▪ Hypotonia or flaccidity
    ▪ Normal muscle stretch reflexes
    ▪ Absent extensor toe sign (Babinski sign)
    ▪ No sensory changes
# Assessment & Grading of Muscle Strength

## REGION | MUSCLE | NERVE ROOT
---|---|---
**Neck** | Trapezius  
Sternocleidomastoid  
Diaphragm | C2, 3, 4  
(cranial nerve 11) C1, 2  
C3, 4, 5

**Shoulder** | Supra- infraspinatus  
Deltoid  
Serratus anterior | C5, 6  
C5, 6  
C5, 6, 7

**Arm** | Biceps, brachioradialis  
Triceps | C5, 6  
C7, 8

**Forearm** | Extensors of wrist  
Extensors of metacarpophalangeal joints  
Flexors of the distal phalangeal joints  
Wrist flexion, radial  
Wrist flexion, ulnar  
Supination  
Pronation | C6, 7, 8  
C6, 7, 8  
C7, 8, T1  
C6, 7  
C6, C7, C8  
C5, 6, 7  
C6, 7

**Hand** | Interossei  
Abductor pollicis brevis | C8, T1  
C8, T1

**Pelvic Girdle** | Iliopsoas  
Gluteus maximus | L2, 3, 4  
L5, S1, 2

**Thigh** | Quadriceps  
Adductors  
Abductors  
Hamstrings, internal  
Hamstrings, external | L2, 3, 4  
L2, 3, 4  
L4, 5, S1  
L4, 5, S1  
L5, S1

**Leg** | Gastrocnemius  
Tibialis anterior  
Peronei | L5, S1, S2  
L4, 5  
L5, S1

**Foot** | Plantar muscles | S1, 2

## Grading reflexes

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent (areflexia)</td>
</tr>
<tr>
<td>1</td>
<td>Hyporeflexia</td>
</tr>
<tr>
<td>2</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>Brisk (normal)</td>
</tr>
<tr>
<td>4</td>
<td>Hyperreflexia (abnormal)</td>
</tr>
</tbody>
</table>

## Grading Strength

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Complete paralysis</td>
</tr>
<tr>
<td>1</td>
<td>Flicker of movement</td>
</tr>
<tr>
<td>2</td>
<td>Moves part only (with gravity “eliminated”)</td>
</tr>
<tr>
<td>3</td>
<td>Moves against gravity</td>
</tr>
<tr>
<td>4</td>
<td>Examiner can overcome action</td>
</tr>
<tr>
<td>5</td>
<td>Normal strength</td>
</tr>
</tbody>
</table>
Clinical Syndromes of Weakness

1. **Diagnostic Categories: Upper motor neuron dysfunction** *(spinal cord involvement)*

2. **Diagnostic Categories: Anterior horn cell dysfunction** *(representative, not an exhaustive listing)*

### Motor neuron disease in children (spinal muscular atrophy)

<table>
<thead>
<tr>
<th>SMA type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SMA type I</strong></td>
<td>Werdnig-Hoffman Disease</td>
</tr>
<tr>
<td><strong>SMA type II</strong></td>
<td>Chronic Werdnig Hoffmann Disease</td>
</tr>
<tr>
<td><strong>SMA type III</strong></td>
<td>Kugelberg-Welander Disease</td>
</tr>
</tbody>
</table>

### Motor neuron disease in adults

<table>
<thead>
<tr>
<th>SMA</th>
<th>Bulbospinal neuronopathy (Kennedys disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X-linked recessive disorder associated with an expanded trinucleotide repeat sequence (CAG) in the androgen receptor gene. More benign prognosis than other motor neuron disease. Clinical characteristics include predominant bulbar weakness (tongue and chin fasciculations), testicular atrophy, diabetes mellitus and gynecomastia.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ALS</th>
<th>(Lou-Gehrig disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chronic degenerative disease of motoneurons in the spinal cord and brainstem. Sensation and cognition remain essentially intact as do eye movements and sphincter function. Usually sporadic, 5-10% of cases are familial.</td>
</tr>
</tbody>
</table>

### Infectious and miscellaneous

| Polio virus infection | Begins with a prodromal phase of fever, myalgia and malaise following an upper respiratory or gastrointestinal syndrome. Neurologic involvement follows and may include aseptic meningitis or a syndrome of weakness and paralysis, usually asymmetric and can involve respiratory and bulbar muscles. The *post-polio syndrome* is characterized as occurring years later, manifested as muscle pain and fatigue and probably representing further aging of a diminished “pool” of anterior horn cells. |
| West Nile virus | While usually presenting as meningoencephalitis, presentations similar to Guillain-Barré as well as an acute paralytic poliomyelitis syndrome have been reported and treatment is primarily supportive |
| Hexosaminidase A deficiency | A type of juvenile or young adult form of motor neuron disease that is secondary to a reduced Hexosaminidase A activity |
3. **Diagnostic Categories: Root lesions**

<table>
<thead>
<tr>
<th>Level</th>
<th>Disc</th>
<th>Primary motor findings</th>
<th>Sensory disturbances</th>
<th>Reflex changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5</td>
<td>C4-C5</td>
<td>Deltoid, Biceps</td>
<td>Lateral upper arm</td>
<td>Biceps</td>
</tr>
<tr>
<td>C6</td>
<td>C5-C6</td>
<td>Biceps, wrist extensors</td>
<td>Lateral forearm, hand and first and second digits</td>
<td>Brachioradialis</td>
</tr>
<tr>
<td>C7</td>
<td>C6-C7</td>
<td>Triceps, wrist flexors, finger extensors</td>
<td>Middle fingers</td>
<td>Triceps</td>
</tr>
<tr>
<td>C8</td>
<td>C7-T1</td>
<td>Hand intrinsic muscles and finger flexors</td>
<td>Little finger, medial forearm</td>
<td></td>
</tr>
<tr>
<td>L4</td>
<td>L3-L4</td>
<td>Quadriceps (knee extension)</td>
<td>Medial calf</td>
<td>Knee (patellar)</td>
</tr>
<tr>
<td>L5</td>
<td>L4-L5</td>
<td>Knee flexion, dorsiflexion of foot</td>
<td>Lateral leg, medial foot, great toe</td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>L5-S1</td>
<td>Hip extension, plantar flexion of foot</td>
<td>Lateral foot, small toe</td>
<td>Ankle (Achilles)</td>
</tr>
</tbody>
</table>

4. **Diagnostic Categories: Plexus lesions**

<table>
<thead>
<tr>
<th></th>
<th>Motor signs</th>
<th>Reflex signs</th>
<th>Sensory signs</th>
<th>Common causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brachial Plexus Lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper plexus paralysis (Erb-Duchenne type)</td>
<td>Muscles supplied by the C5 – C6 roots (axillary and musculocutaneous nerve)</td>
<td>Biceps and brachioradialis are depressed or absent</td>
<td>Sensory loss over the deltoid muscle</td>
<td>Trauma (sports related “stingers”), birth injury, idiopathic (Parsonage-Turner syndrome), Radiation-induced injury</td>
</tr>
<tr>
<td>Middle plexus paralysis</td>
<td>Muscles supplied by C7 nerve roots (radial nerve)</td>
<td>Triceps reflex may be absent</td>
<td>Sensory loss over the extensor surface of the forearm and dorsum of the hand</td>
<td>Uncommon and usually from trauma</td>
</tr>
<tr>
<td>Lower plexus paralysis (Dejerine-Klumpke type)</td>
<td>Muscles supplied by C8 and T1 nerve roots (ulnar nerve)</td>
<td>(Finger flexor reflex, C8-T1, may be lost)</td>
<td>Sensory loss over the medial arm, forearm and hand and may have a ipsilateral Horner syndrome</td>
<td>Usually traumatic (arm traction in abducted position) Metastatic involvement (Pancoast tumor)</td>
</tr>
</tbody>
</table>

**Lumbosacral plexus lesions**

| Lesions of the lumbar segments | Muscles supplied by L1-L4 nerve roots (femoral and obturator nerves) | Knee (patellar) reflex may be depressed | Sensory loss over the lateral anterior and medial thigh, medial leg | Neoplasm’s, radiation therapy induced, retropertoneal hemorrhage, surgery, diabetes (Syndrome of diabetic amyotrophy) |
| Lesions of the sacral segments | Muscles supplied by L4 – S1 nerve roots (superior and inferior gluteal nerves and sciatic nerve) | Ankle (Achilles) reflex | Sensory loss over the outer leg, dorsum of the foot (If pudendal nerve injury; impairment of rainy bladder or bowel control | Neoplasm’s, radiation therapy induced, retropertoneal hemorrhage, surgery, diabetes (Syndrome of diabetic amyotrophy), labor and delivery |
### 5. Diagnostic Categories: Peripheral nerve (representative examples, not an exhaustive listing)

#### Mononeuropathies: Upper Extremity

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Entrapment Site</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median nerve</td>
<td>Entrapment in the carpal tunnel</td>
<td>Numbness and tingling involving the first four digits, but discomfort that can also be experienced in the forearm and shoulder. Frequently exacerbates with activity or at night and patients often seek relief by &quot;flicking&quot; their wrist. When severe, there can be weakness and atrophy of the thenar muscles.</td>
</tr>
<tr>
<td>Ulnar nerve</td>
<td>Entrapment in the cubital tunnel</td>
<td>Numbness and tingling of the ulnar division of the hand, but pain can be experienced within the forearm and elbow. Weakness includes the interossei, hypothenar muscles of the hand, and the flexor digitorum profundus; when severe there is an ulnar clawhand deformity (sign of benediction)</td>
</tr>
<tr>
<td>Radial nerve</td>
<td>Entrapment in the spiral groove</td>
<td>Sensory loss involves the dorsum of the hand, thumb and index finger. Weakness includes the radial innervated muscles of the upper extremity and difficulty with extension of the wrist, fingers and thumb (the triceps can be spared) and resulting in a wrist-drop.</td>
</tr>
</tbody>
</table>

#### Mononeuropathies: Lower Extremity

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Entrapment Site</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroneal nerve</td>
<td>Entrapment at the fibular head</td>
<td>Most patients present with a foot-drop and sensory loss is frequently minimal, but if present it is over the dorsum of the foot and toes and can extend along the lateral leg. In addition to weakness of ankle and toe dorsiflexion, ankle eversion is weak as well.</td>
</tr>
<tr>
<td>Lateral femoral cutaneous nerve</td>
<td>Entrapment at the inguinal ligament</td>
<td>Syndrome of pain and a burning or &quot;crawling&quot; sensation accompanied by a decrease in pin sensation along the anterolateral thigh - meralgia paresthetica. Strength and the patellar reflex are normal. This usually exacerbates with activity and the patient frequently rubs the area for relief</td>
</tr>
</tbody>
</table>

#### Polyneuropathy

Symptoms of a polyneuropathy usually begin with tingling or numbness of the feet and fingers. Typically pinprick and touch sensation are lost first and resulting in the stocking and glove pattern of sensory loss (usually sensory symptoms within the hand are not obvious until lower extremity sensory loss reaches the knees). If position sense loss occurs, then a sensory ataxia can appear. Weakness and wasting is usually distal and involving the lower extremities first; muscle stretch reflexes are usually lost as well. Polyneuropathies are usually due to either axonal degeneration or less frequently demyelination and those pathological features are used in their classification.

#### Pattern Recognition of (Poly)neuropathies

(Your diagnosis is “focused” by a clinical classification that considers the distribution of weakness, nature of sensory involvement, absence of upper motor neuron signs, temporal evolution and checking for evidence of a hereditary basis)

<table>
<thead>
<tr>
<th>Symmetric proximal and distal weakness with minimal sensory loss</th>
<th>Guillain-Barré syndrome*</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Guillain-Barré syndrome: An autoimmune disorder frequently preceded by a viral or bacterial illness. Often accompanied by aching pain and subsequently followed by ascending weakness of the extremities and areflexia; sensory loss is usually minimal, but autonomic symptoms are often present. The disorder reaches its nadir in 2 weeks and severe weakness and respiratory failure can occur. Diagnosis is further established by CSF exam (high protein and acellular) and EMG testing which demonstrates a pattern of acquired demyelination of the nerves. Treatment hastens recovery and consists of either plasmapheresis or IVIG administration.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symmetric distal weakness with sensory loss</th>
<th>Metabolic, drugs/toxins, hereditary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymmetric distal weakness and sensory loss</td>
<td>Multiple nerves: Vasculitis, HNPP, infectious Single nerves: Compressive, radiculopathy</td>
</tr>
<tr>
<td>Asymmetric distal weakness without sensory loss</td>
<td>Motor neuron disease, Multifocal Motor Neuropathy</td>
</tr>
<tr>
<td>Asymmetric proximal and distal weakness with sensory loss</td>
<td>Diabetes, HNPP (Hereditary neuropathy with predisposition to pressure palsies), infiltrative (carcinomatosis), metabolic, drugs/toxins, hereditary</td>
</tr>
<tr>
<td>Symmetric sensory loss without weakness</td>
<td>Metabolic, toxins, drugs, cryptogenic</td>
</tr>
<tr>
<td>Asymmetric proprioceptive sensory loss without weakness</td>
<td>Ganglionopathy: Cancer (paraneoplastic), Sjögrens, cisplatin, B6 toxicity, HIV, idiopathic</td>
</tr>
<tr>
<td>Autonomic symptoms and signs</td>
<td>Diabetes, amyloidosis, HIV, porphyría, GBS variant idiopathic pandyautonomia</td>
</tr>
</tbody>
</table>
6. Diagnostic Categories: Neuromuscular junction and Myopathies

**Myasthenia Gravis**
This is an autoimmune disorder where antibodies to the post-synaptic acetylcholine receptor occur. More common in females than men and presenting with fluctuating weakness with easy fatigability. The predilection for extraocular, facial, masticatory and bulbar muscles results in their early dysfunction. Extremity weakness is common and usually more obvious in a proximal distribution. There is a frequent association with thymic tumors, and thyroid disorders; certain classes of medications may worsen symptoms (quinine, phenytoin, aminoglycoside antibiotics). Diagnosis is established both through electrophysiological evaluation where a classic **decremental response** of the motor response is seen with repetitive stimulation as well as detection of the acetylcholine receptor antibody in serum samples. The association with thymic tumors necessitates evaluation for their presence.

**Myasthenic syndrome (Lambert-Eaton syndrome)**
A paraneoplastic syndrome caused by antibodies to the voltage gated, pre-synaptic, calcium channels that are involved in acetylcholine release at the neuromuscular junction. It presents with proximal weakness, similar to MG, but the extracranial muscles are usually not involved. Autonomic disturbances, dry mouth, constipation and impotence are also present. The disorder can be identified by electrophysiologic testing, where a classic **incremental response** is seen after repetitive nerve stimulation on EMG as well as the identification of serum antibodies to the calcium channel.

**Botulism**
Caused by ingestion of the toxin produced by *Clostridium botulinum* and usually from contaminated food (a different clinical syndrome is seen in children who ingest spores of the bacilli). Weakness begins in 12-72 hours and manifested as diplopia, facial weakness, dysphagia, nasal speech, and difficulty with respiration, limb weakness develops later. Autonomic symptoms are common, but there are no sensory symptoms and reflexes usually stay intact.

<table>
<thead>
<tr>
<th>Hereditary myopathies</th>
<th>Acquired myopathies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Muscular dystrophies</strong></td>
<td>Distinguished by their hereditary basis, clinical presentation and progressive nature</td>
</tr>
<tr>
<td><strong>Inflammatory</strong></td>
<td>Polymyositis, Dermatomyositis and Inclusion body myositis would fit into this group as would some forms of AIDS related myopathy</td>
</tr>
<tr>
<td><strong>Myotonias</strong></td>
<td>Characterized by delayed relaxation of muscles and the clinical or EMG finding of myotonia. They may be &quot;benign&quot; or progressive (such as myotonic dystrophy)</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td>Disorders of thyroid, parathyroid, adrenal and pituitary function can all result in muscle dysfunction</td>
</tr>
<tr>
<td><strong>Channelopathies</strong></td>
<td>A group of disorders caused by mutations in genes coding cell membrane ion channels. This includes some of the Myotonias as well as hypo- or hyperkalemic periodic paralysis</td>
</tr>
<tr>
<td><strong>Associated with systemic disease</strong></td>
<td>Polymyalgia Rheumatica could be included here</td>
</tr>
<tr>
<td><strong>Congenital myopathies</strong></td>
<td>Rare and non-progressive they usually begin in infancy or childhood and are associated with weakness, hypotonia and a normal creatinine kinase level. Many are inherited and they are classified based on histopathologic features</td>
</tr>
<tr>
<td><strong>Drug-induced</strong></td>
<td>Precipitated by medication use (i.e., Lipid lowering, colchicine, AZT)</td>
</tr>
<tr>
<td><strong>Metabolic myopathies</strong></td>
<td>Result from insufficient energy related to defects in glycopigen, lipids, adenine nucleotides or mitochondrial metabolism</td>
</tr>
<tr>
<td><strong>Toxic myopathies</strong></td>
<td>Perhaps the most common toxic cause is excessive ethanol use</td>
</tr>
<tr>
<td><strong>Mitochondrial myopathies</strong></td>
<td>Clinically heterogeneous group of disorders that are associated with defective oxidative phosphorylation and often structural abnormalities of mitochondria with <strong>ragged red fibers</strong> seen on muscle biopsy</td>
</tr>
</tbody>
</table>

Questions to ask that will aid in helping to classify a suspected myopathy.
1. Does the patient have "**positive**" symptoms (myalgia, cramp, contractures, stiffness, inability to relax, hypertrophy) or "**negative**" symptoms (weakness, fatigue, exercise intolerance, muscle atrophy)?
2. What are the temporal characteristic of their weakness, pain or stiffness?
3. What is the distribution of weakness?
4. Are there triggering events for episodic weakness, pain, stiffness?
5. Is there a family history of a myopathic disorder?
6. Are their associated medical conditions?
Diagnostic Tools or Investigations

- **Diagnostic Tools:**
  - **History and examination**
    - The most important aspect of the successful evaluation of a patient and the one component we usually “short change”
  - **Neuroradiological imaging**
    - If localization includes a site within the central nervous system, then imaging of the brain or spinal cord allow us to clarify and confirm our tentative diagnosis. MRI with and without gadolinium have replaced CT scanning in most circumstances. The role of PET, SPECT and other nuclear radioisotope imaging studies are being delegating to more focused and limited indications.
    - When clinical localization includes the need to evaluate a limb or the retroperitoneum, then CT as well as MRI imaging are of use and especially when a mass lesion is being excluded.
  - **Electrodiagnostic studies**
    - **EMG studies** are of help in regards to disorders of the neuromuscular system and in general considered an extension of the clinical exam. When ordered they should be accompanied by a clinical question or the need to clarify a clinical diagnosis (i.e., Is this patients’ symptoms of weakness and numbness secondary to a nerve entrapment, CTS, or evidence of a cervical radiculopathy?). A non-specific request will usually lead to an unclear and unfocused evaluation and hence not serve the best interests of you or your patient.
    - **Evoked Potentials** are studies that evaluate the function of the central nervous system and usually performed with the hope of identifying an abnormality that impacts’ on transmission of sensory information. They have found their greatest diagnostic use in evaluating patients with multiple sclerosis by demonstrating delays in transmission of sensory information (somatic-sensory by somatosensory evoked potentials (SSEP), visual by visual evoked potentials (VEP) and finally auditory by brainstem auditory evoked responses (BAER)). All serve as paraclinical tests that help to establish a diagnosis and identify symptomatic or asymptomatic CNS involvement.
  - **Laboratory evaluations (These need to be guided by the clinical impression)**
    - Routine studies would include those often obtained in the evaluation of metabolic disorders, such as a CBC, chemistry profile or a glycosylated hemoglobin level and in many presentations of weakness they provide the greatest amount of diagnostic information.
    - Lumbar puncture is used less frequently as other diagnostic studies appear to be more sensitive and helpful in establishing a diagnosis. However, it is a test with few complications and in some cases (Guillain-Barré syndrome) provides diagnostic confirmation.
    - Specialized laboratory studies include those that provide: support for a diagnosis (Acetylcholine receptor antibody when evaluating for myasthenia gravis), an unusual disorder is suspected (Sjögrens disease in someone presenting with a sensory neuropathy), a serious disorder is presenting with neuromuscular symptoms (such as a lung cancer where the presentation is Lambert-Eaton myasthenic syndrome), clarify a diagnosis of muscular dystrophy (imunoanalysis of a muscle biopsy) or screening family members for a suspected hereditary neuropathy (genetic sequencing).
  - **Tissue examination (This needs to be guided by the clinical impression)**
    - Muscle and Nerve biopsy are performed where an inflammatory process is suspected, a specific diagnostic abnormality is being sought or if tissue is needed in order to complete more extensive biochemical or histopathologic studies. In many cases, less invasive studies serve the same purpose, but if a biopsy is performed then the tissue needs to be examined in a medical center that is well versed in its proper interpretation and handling.

**SUGGESTED REFERENCES (If you are really interested)**

- Rosow LK, Amato AA. *The role of electrodiagnostic testing, imaging, and muscle biopsy in the investigation of muscle disease.* Continuum (Minneap Minn) 2016;22(6):1787–1802.

Neuromuscular Disease Center – Washington University, St. Louis, MO; USA: [http://neuromuscular.wustl.edu/](http://neuromuscular.wustl.edu/)