667

Neuromuscular Diseases

Muscle Diseases (Myopathy)

Dermatomyositis (DM): DM is an *auto immune* muscle disease which occurs in children and adults. The cardinal sign of this disorder is the presence of a rash commonly over the upper chest and back or shoulders. Occasionally, a purplish (heliotrope) discoloration is present over the eyelids. Along with the rash, muscle weakness in the hips and shoulders is noted. The disease develops over weeks to months. The cause is unknown but involves inflammation of the blood vessels in the skin and muscle. Diagnosis is clinical with supportive evidence from blood levels of muscle enzymes (*CK or creatine kinase*), and EMG findings. Many people undergo muscle biopsy for a definitive diagnosis. The disease responds well to oral *steroids* but is sometimes resistant and may require treatment with azathioprine or *IVIG.*

Polymyositis (PM)*:* PM is similar to *DM* but doesn't have the rash. Symptoms develop over weeks to months in most cases. The cause is usually unknown but occasionally, PM and DM are associated with cancer or rheumatoid conditions. Treatment is similar to that of DM.

Drug-induced myositis: Several medications may lead to muscle damage. These include certain cholesterol lowering agents, colchicine, and ipecac.

Inclusion Body Myositis (IBM): IBM develops more slowly than either *PM* or *DM.* Typically, a diagnosis is not reached for several years. Weakness is more asymmetric and there is no rash. The cause is unknown but may represent a degenerative condition with secondary inflammation as opposed to PM where inflammation is primary. Perhaps because of this, IBM responds less well to *steroids* and other immune suppressing therapies.

Muscular Dystrophy

Duchenne's muscular dystrophy (DMD): DMD is a progressive hereditary disease that presents in boys during infancy or early childhood. Affected children will be slow to walk and may fail to master certain motor activities by the appropriate age. Initially, patients have weakness in shoulder and hip girdle muscles initially but, over years, become weak in hand and foot muscles as well as respiratory and cardiac muscles. The disease progresses to death often by the age of 20 due to heart failure or respiratory compromise. A severe deficiency or absence of the protein dystrophin underlies this disease but the exact mechanism is unknown. Diagnosis is clinical with supportive evidence from *EMG* and *CK* elevation. Definite diagnosis is now possible

by muscle biopsy or by genetic testing of blood. The disease partially responds to high doses of oral *steroids* but there is no cure. A milder form of DMD is known as Becker dystrophy and results from a partial loss of dystrophin. In some cases, women who carry the abnormal gene have some mild symptoms of muscle disease (cramps, slight weakness, mildly elevated CK) and are known as manifesting carriers.

Limb-girdle dystrophy(LGD): LGD may be a severe muscle disease beginning in infancy or becoming noticeable only during adulthood depending on the variety. In some cases there is an abnormality of a muscle membrane protein related to dystrophin (see *DMD*). Weakness is predominately located in the shoulder and hip girdle muscles. In affected adults the disease progresses slowly and is usually not life-threatening. This disease is inherited in some cases and there is no known treatment.

Myotonic dystrophy (DM): Unlike most muscular dystrophies, DM usually shows severe distal weakness prior to the development of proximal weakness. It is inherited in a dominant fashion (meaning an affected person has a 50% chance of passing the disease to each of his or her children). Symptoms can be evident at birth or not be noticeable until adulthood. Drooping of the eyelids (ptosis), swallowing muscles and cataracts are other frequent features of the disease. No cure or effective treatment is available.

Diseases of the Neuromuscular Junction

Myasthenia gravis (MG): *Auto immune* disease where the target of inflammation are the *acetylcholine receptors* on the muscle membrane. MG may occur at any age and common early symptoms are double vision, droopy eyelids, difficulty swallowing, or generalized weakness. The onset may be gradual over months or develop rapidly over several days or weeks. Diagnosis is clinical with supportive evidence including presence of acetylcholine receptor antibodies, positive tensilon test, or abnormal electrodiagnostic testing. A number or therapeutic agents are available and include *steroids*, *IVIG*, *plasmapheresis*, azathioprine, pyridostigmine and surgical removal of the thymus gland.

Acquired Nerve Diseases (Polyneuropathies)

Axonal Polyneuropathies

Diabetic polyneuropathy occurs in many patients with either insulin-dependent or non-insulin dependent diabetes mellitus. It's severity can be correlated to some degree with the severity and duration of hyperglycemia. The disease has a predilection for small *unmyelinated* nerve fibers which carry information on temperature and pain so that the early symptoms are reduced pain awareness and the inability to detect temperature. Paradoxically, the symptoms tend to be associated with burning of the toes or bottom of the foot. The symptoms develop symmetrically and often spare the hands. Significant weakness is unusual although it can be quite painful. Diagnosis is clinical and may be confirmed with *NCS*. Other causes may need to be ruled out. There are many medicines that ameliorate the pain (amitriptyline, nortriptyline, gabapentin, carbamazepine, capsaicin) but these do not treat the underlying neuropathy. A human

protein called Nerve Growth Factor (NGF) may help treat the underlying neuropathy and reduce the symptoms. NGF is being studied in a clinical research trial at BGSM and other centers around the country. *Click here* for information on this study.

Vitamin B12 deficiency may lead to a number of serious conditions including peripheral neuropathy. This may occur in persons who are strict vegetarians, people who are malnourished, and may also happen to otherwise healthy people on normal diets who develop pernicious anemia. In this *auto immune* disease, the body makes antibodies against its own cells in the gut lining which leads to an underproduction of intrinsic factor, the protein which is responsible for binding B 12 in the intestine and getting the vitamin into the bloodstream. Absence of the vitamin leads to anemia which is resistant to iron therapy and may cause neuropathy and a more serious condition of degeneration in the spinal cord called subacute combined degeneration. This may occur in addition to neuropathy and causes weakness, sensory loss and incoordination. The peripheral neuropathy of vitamin B12 is not unusual and presents with tingling/numbness in the feet sometimes associated with more painful altered sensations (dysesthesias). Weakness is uncommon except in cases where there is concomitant subacute combined degeneration. The diagnosis is confirmed by NCS and by testing the blood vitamin B12 level. One important point that is overlooked is that many patients with neuropathy from B12 deficiency do not have the anemia or changes in the white blood cells that frequently seen in this disorder. Treatment is with vitamin B12 injections or oral therapy depending on the severity of the deficiency and the underlying cause. Treatment may not be successful in completely restoring the nerves to pre-deficiency function.

Neuropathies associated with paraproteins: Paraproteins are abnormal proteins in the blood which are sometimes markers for malignancy but maybe of benign origin. Sometimes these are associated with nerve disease and cause a wide range of symptoms from severe sensory involvement to primarily weakness. These neuropathies are much more common in the older age groups (>60 yrs) and are often of mild severity. The neuropathy is slowly progressive but occasionally progresses more rapidly. The symptoms can be treated with medicines that ameliorate the pain (amitriptyline, nortriptyline, gabapentin, carbamazepine, capsaicin) but this doesn't affect the underlying neuropathy. When the disease is severe, treatment of the nerve disease can be attempted with *steroids* and other immunosuppressants.

Neuropathies associated with thyroid disease: There is an association between hypothyroidism and polyneuropathy. When it does occur the symptoms are typical of all neuropathies: tingling/burning and sharp, sudden, lancinating pain in the feet and hands. More commonly, *carpal tunnel syndrome* is a presentation of hypothyroidism.

Toxic neuropathies: Many drugs are known to cause neuropathy. The most common are the chemotherapeutic agents vincristine, cisplatinum, taxol. Some others include cyclosporine, metronidazole, dapsone, and amiodarone. Pesticide exposure can cause neuropathy. Rarely, heavy metal intoxication (lead, arsenic, mercury) can cause neuropathy.

Alcoholic neuropathy: Heavy alcohol use may cause a neuropathy which is mostly sensory. Burning and tingling in the feet is first noted and the involved area may ascend over months to years. Abstention from alcohol use may alleviate the symptoms and will

prevent further nerve deterioration.

Cancer-associated: Neuropathies of all types may be associated with cancer and are known as paraneoplastic neuropathy. One special condition should be mentioned. A rapidly progressive symmetric or asymmetric purely sensory neuropathy may be the first indication of certain tumors usually small cell lung tumors. *NCS* can make the diagnosis of pure sensory neuronopathy but further testing would need to be performed to determine if the cause was a malignancy. Treatment of the malignancy may improve the neuropathy.

HIV (AIDS) associated neuropathy: Many types of neuropathy are associated with HIV infection. The most common is a painful, symmetrical neuropathy affecting the feet. Patients usually complain of burning, tingling and altered sensation. Treatment is difficult and includes nortriptyline, carbamazepine, and gabapentin.

Demyelinating Polyneuropathies

Acute Inflammatory Demyelinating Polyneuropathy (Guillain-Barre Syndrome): AIDP starts with tingling in the legs and arms, sometimes mild weakness or difficulty walking, and is associated with back pain in roughly half of the cases. Over hours to several days the neuropathy progresses to cause numbness and weakness throughout the body. The nerves that control breathing, heart rate, and eye movements can be involved necessitating hospital admission. The cause of the condition is unknown but is believed by many doctors to be an *auto immune* disease triggered by the body's response to an infection. Most commonly, there is inflammation of the *myelin*, the nerve coating, but preservation of the nerve fiber is such that even in severe cases the long term prognosis for significant improvement is quite good. Diagnosis is clinical but is supported by *NCS* and spinal tap findings. The course of the disease is shortened by treatment with *IVIG* or *plasmapheresis*. *Steroids* do not appear to be of value in this disease. This disease has a distinct, rapid presentation and is a life-threatening condition. If you think you have this YOU SHOULD NOT BE WASTING YOUR TIME SURFING THE WEB.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP): Like AIDP, there is inflammation of the *myelin* in this disease but the course of the illness is usually much slower. Symmetrical or asymmetrical numbness and tingling in the feet with or without weakness are often the first symptoms. The disease may be slowly progressive or can wax and wane. The cause is unknown. Most cases are *idiopathic* but the disorder is sometimes associated with *paraproteins*, HIV, and cancer. Diagnosis is confirmed by *NCS*. First-line treatment is with *steroids* or *IVIG*. *Plasmapheresis* may be used in more severe cases. Other treatment includes azathioprine or cyclosporine.

Hereditary Peripheral Neuropathies

Hereditary Motor and Sensory Neuropathy: (Charcot-Marie-Tooth disease) This is the most common type of inherited neuropathy. There are 2 main types: *demyelinating* (type 1) and *axonal* (type 2) although it usually not possible to differentiate them without nerve conduction studies (*NCS*) or genetic testing. The

inheritance is dominant meaning a person with CMT has a 50% chance of passing it down to each of his or her children. Typically, CMT patients have unusually high arches noted from early in life but are normal into the teenage years. CMT children frequently turn their ankle and may be "clumsy" as they trip over their toes frequently. Sometimes the disease isn't recognized until patients are much older (40-60 yrs). Commonly, CMT patients complain of weakness more than numbness/tingling/burning despite profound involvement of their sensory nerves. The disease is slowly progressive and, although many patients need to wear a brace to help keep their feet from dragging, most patients are not disabled or wheelchair bound and have a normal life expectancy. Research has shown that the most common form of CMT (Type 1A) is caused by an overexpression of a *myelin* gene, PMP-22. The exact function of this protein is currently unclear and there is no current treatment for the underlying disease.

Hereditary Neuropathy with Liability to Pressure Palsies (HNPP): This disease is probably widely under diagnosed. Like *CMT Type 1A*, it is a *demyelinating* neuropathy and may be the result of an under dosage of a *myelin* protein (PMP-22) which is overproduced in CMT 1A. This disease should be considered in patients with multiple *entrapment neuropathies* as these are common in HNPP. Symmetrical burning/numbness/tingling in the feet may also be present. As in CMT, the exact cause is unknown and there is no treatment other than pain medicines and avoidance of entrapment neuropathies.

Entrapment (Compression) Neuropathies

Carpal Tunnel Syndrome (CTS): CTS is the most common entrapment neuropathy. Persons with CTS complain of tingling or numbness in their fingers especially the thumb, index and middle fingers. Occasionally, the tingling is irritating and awakens people from sleep or bothers them when they read the newspaper. Weakness is unusual but people often complain of dropping things if they aren't looking at them. CTS is caused by irritation of the median nerve as it passes from the middle of the wrist into the palm through a tunnel created by ligaments and bones called the carpal tunnel. CTS can be easily diagnosed by NCS and is treated with splinting the wrist at night in mild cases or surgical release of the ligaments which form the roof of the tunnel in more severe cases.

Ulnar Neuropathy at the Elbow: Another common entrapment neuropathy, this disorders typically begins with elbow pain with tingling ("hit your funny bone" sensation) in the ring finger and little finger. If the condition is left untreated, grip strength becomes reduced and the muscles of the hand may *atrophy* causing the tendons and bones to appear more prominent. Here, the ulnar nerve is irritated as it passes between two bones along the inside of the elbow (ulnar groove). This is also diagnosed with *NCS/EMG* and can be treated with splinting and padding the elbow, or with surgery. The surgery is more involved than in *CTS* as the nerve is typically moved out from the bones and is placed in the forearm.

Tarsal Tunnel Syndrome: This neuropathy is less common than the others and is more difficult to treat and diagnose. Tingling or pain along the toes and bottom of one foot is the most common presentation. Weakness of foot muscles is rare and it is unusual for the symptoms to be in both feet. Ankle injuries may predispose people to have such symptoms. The tibial nerve is irritated as it passes between the Achilles

tendon and the prominent bone at the inside of the ankle. *NCS* is occasionally useful in making the diagnosis but specialized testing may be necessary. In severe cases, surgeons can decompress the tibial nerve at the ankle by cutting the overlying ligaments. Surgery is less successful than in *CTS*.

Peroneal neuropathy at the knee: This usually occurs in people who cross their legs or squat for prolonged periods of time like gardeners. All of these maneuvers compress or stretch the peroneal nerve as it crosses over a bone (fibula) along the outside of the knee. Trauma is another common reason to develop this problem. People may become unable to flex their ankle upward (*foot drop*). Occasionally, there is also numbness along the outer portion of the calf or top of the foot. The weakness usually goes away by itself if the leg-crossing and squatting is discontinued. Surgery is rarely necessary.

Sciatic neuropathy: The sciatic nerve forms from after nerve roots from the lower lumbar and sacral spine participate in the plexus. The nerve has 2 divisions (peroneal and tibial) which divide behind the knee. Sciatic neuropathy would be an uncommon cause of "*sciatica*" and is most often seen in the setting of hip fractures or hip surgeries. Severe motor vehicle accidents and penetrating trauma also cause sciatic neuropathies. On occasion, these occur following improper placement of an intramuscular injection into the buttock. The so-called "wallet-neuropathy" produces mild sciatic symptoms after prolonged sitting on a hard surface. In this setting, generally male patients may complain of tingling/numbness on their feet or calves and with a mild *foot drop*. Wallet neuropathy resolves spontaneously after switching the wallet to the other pocket.

Nerve Plexus Diseases

Brachial plexopathy: The brachial plexus is a complicated network of nerves in the shoulder. These are commonly damaged in several settings including birth trauma, severe motor vehicle accidents and penetrating trauma (bullet and stab wounds), and due to lung and breast malignancies. Sometimes these occur without clear reason (*idiopathic*) and are called idiopathic brachial plexopathy. There are a variety of names for this disorder including neuralgic amyotrophy, Parsonage-Turner syndrome or brachial plexitis. The cause is unknown but may be *auto immune* or post-viral as this disorder often follows surgery or viral infections. Severe shoulder pain heralds the disease and may last for days to weeks. Following this, people may notice weakness, numbness, or *atrophy* of their muscles. Usually, there is spontaneous improvement without specific treatment. Some experts recommend a short course of oral steroids if the process is caught early while there is still pain.

Lumbosacral plexopathy: The lumbosacral plexus is a complicated network of intertwining nerves located in the pelvis. These nerves may be damaged following severe trauma or occur in relation to hip/pelvic surgeries. Occasionally, a hematoma from a catheterization procedure causes a plexopathy. *Idiopathic* lumbosacral plexopathies are much less common than idiopathic brachial plexopathies but may occur. One special type of lumbosacral plexopathy should be mentioned is *diabetic amyotrophy*.

Diabetic amyotrophy: This disorder is often seen in recently diagnosed diabetics

and may be the first sign of the disease. Typically, there is the development over hours to days of severe pain in the groin and upper thigh followed by weakness of bending the hip and/or straightening the knee. The muscles of the upper leg may become *atrophied*. The disease may progress for some weeks then commonly improves spontaneously over months. Occasionally, amyotrophy occurs bilaterally. The cause is unknown but may be vascular in nature. To date there has been no treatment for this disease, although there are reports of *IVIG* and oral *steroids* being effective.

Nerve Root Diseases (Radiculopathy)

Cervical radiculopathy: Impingement of bone or disk material on a cervical nerve root can cause neck pain which radiates into the arm, weakness of arm and shoulder muscles, and numbness. The most common cervical radiculopathy is C6-7 which may cause neck/arm pain, weakness of the triceps, and numbness in the middle fingers. The C5-6 root tends to cause numbness in the thumb and index finger in association with deltoid and biceps weakness. The C7-8 root may cause numbness in the ring and little fingers in association with decreased grip strength or fine coordination of the fingers. If the symptoms are mild, no diagnostic testing may be necessary. If severe, an MRI scan of the neck and/or an *EMG* are helpful in confirming the diagnosis. Conservative therapy consists of warm compresses, cervical collar, physical therapy and occasionally traction. Surgery may be performed to decompress the nerve root by a neurosurgeon or orthopedic surgeon.

Lumbosacral radiculopathy: This is sometimes known as *sciatica*. Impingement of bone or disk material on a nerve root in the low back can cause pain which radiates into the hip, buttock, and leg. Numbness and weakness may also occur. The most common roots to be affected are the L4-5 and L5-S1 roots. L4-5 radiculopathies present with back pain, numbness on the outside of the calf and sometimes weakness of flexing the ankle upwards or *foot drop*. S1 root disease often causes numbness on the back of the calf and bottom of the foot associated with weakness on pointing the toe. If the symptoms are mild, no diagnostic testing may be necessary. Most low back pain resolves spontaneously within 2 weeks and current recommendations are to continue with your normal activities as much as can be tolerated. Prolonged bed rest should be avoided. Low back pain associated with weakness is more serious and an MRI scan of the lower back and/or and *EMG* are helpful in confirming the diagnosis. Conservative therapy consists of non-steroidal medications (such as ibuprofen), heating pads and physical therapy. A neurosurgeon or orthopedic surgeon can decompress the nerve root in the operating room.

Degenerative Disk Disease: As people age, the intervertebral disks become less pliable and more calcified like bone. Years of stress on the vertebrae cause constant breakdown followed by build up of new bone at the point where the vertebrae touch each other. The condition can mimic *cervical* or *lumbosacral radiculopathies*. Bony overgrowth may narrow the openings for the nerve roots (foramina) and will diminish the size of the spinal canal. This condition is called cervical stenosis in the neck and lumbosacral stenosis in the low back. The process can be accelerated through trauma, arthritis, obesity, and years of physical labor.

Cervical stenosis often presents with neck pain with or without radiation into the arms and with difficulty walking due to poor balance or leg stiffness/weakness. The

diagnosis is clinical with supporting evidence from a cervical MRI scan or myelogram. If symptoms are mild, it can be treated with non-steroidal medications or sometimes with epidural injection of *steroids*. More severe symptoms can be treated with decompressive surgery.

Lumbosacral stenosis often presents with low back pain sometimes with radiation into the buttock or leg(s) but weakness is uncommon. Some patients with this disorder will have cramps (neurogenic claudication) in their calves or thighs. Sometimes symptoms can be relieved by bending over and flexing the spine forward. Back pain due to stenosis may also improve on walking as opposed to back pain from *lumbosacral radiculopathy* which may worsen with movement. The diagnosis is clinical with supporting evidence from an MRI scan or myelogram. If symptoms are mild, it can be treated with non-steroidal medication or sometimes with epidural injection of *steroids*. More severe symptoms can be treated with decompressive surgery.

Motor Neuron Disease

Motor Neuron Diseases are a group of diseases which are unified by their selective involvement of *upper and or lower motor neurons*. There are likely to be multiple causes for these diseases even within the groupings listed below. Some points in common are that MNDs tend to relatively spare eye movements and bladder/bowel function.

Amyotrophic Lateral sclerosis (ALS) or Lou Gehrig's Disease: This disease affects both upper (UMN) and lower (LMN) motor neurons (see *principles of neuroanatomy*) producing progressive *spasticity*, weakness, and *atrophy* of the limb muscles. Typically, the disease begins with painless weakness and wasting of the muscles of one hand or one foot. Sensory complaints should not be present but muscle twitching or fasiculations may be noted. Another common presentation of this disease is the gradual onset of difficulty speaking (dysarthria) or swallowing (dysphagia). This is due to involvement of the *bulbar* muscles. The disease is progressive at a variable rate but is often marked by plateaus and extremely rare reports of spontaneous regression. Depending on the age of onset and the type of presentation, the average life expectancy is around 3 years. Some people live much longer with approximately 10% surviving longer than 10 years. The cause of this disease is unknown. Diagnosis is clinical with supportive evidence from NCS/EMG. Frequently, MRI scans of the brain or spine are necessary to rule out tumors or degenerative spine disease. Riluzole is the first drug to receive FDA approval for the treatment of ALS. The drug has been shown to extend the life expectancy of patients by several months.

There are several clinical syndromes that may be related to ALS but can also be caused by other disorders. They are named according to the type of motor neurons which degenerate. Progressive Muscular Atrophy (PMA) involves only LMNs, Pseudobulbar Palsy affects the UMNs of the face and throat muscles, Progressive Bulbar Palsy involves LMNs of the face and throat muscles.

BGSM is actively involved with ALS and, frequently, the physicians at BGSM are involved with clinical trials of experimental agents. *Click here* for an update on current research protocols offered at BGSM. Basic scientists at BGSM are also actively

involved with the study of motor neuron development and survival.

Multifocal motor neuropathy with conduction block: This recently described disease may mimic *ALS*. Usually, there is a very slow development of weakness and wasting in one hand or arm with minimal sensory changes. UMNs do not degenerate in this disease. *NCS* may show conduction block, an electrophysiologic finding that suggests focal *axon* dysfunction or *demyelination*. This disease can respond dramatically to *IVIG*.

Polio: Unlike all the other motor neuron diseases considered here, polio has an abrupt onset, is self limited and improves spontaneously. Polio is caused by infection with the polio virus which begins with fever and lethargy and progresses to paralysis of all or some of the muscles. The majority of cases occur in infants and can occur following administration of the oral polio vaccine (OPV). The risk of contracting polio from the vaccine is 1 in 2.5 million. Recovery may be full or partial depending on the degree of *LMN* degeneration. Adults who suffered polio as a child frequently have scoliosis of the spine and atrophy of one or more limbs. These patients may develop a variety of symptoms (weakness, fatigue, pain) years after their infection known as the post-polio syndrome.

Spinal Muscular Atrophy (SMA): There are a variety of SMA disorders which affect infants and adults. These disorders affect only *LMN*s and in adults are very slowly progressive. One of the SMAs that can mimic ALS is Kennedy's disease or X-linked Spinobulbar Muscular Atrophy. As the disorder is linked to a gene on the X-chromosome and is *recessive*, only males will get the disease and females are carriers. Kennedy's Disease is marked by proximal weakness in the limbs and by weakness of facial muscles. Other features include a sensory neuropathy, decreased fertility, and enlarged breasts. This disease does not shorten life expectancy but may result in mild to moderate disability. [go to *featured topics*].

Monomelic amyotrophy: This rare form of MND usually affects one arm with weakness and wasting and occurs mostly in males in their teenage or early adult years. The disease may progress rapidly for 1-2 years then very slowly progress or halt with minimal recovery. This should not be confused with *ALS*. [ref Donofrio's article]