

## Neuropathy, Myopathy, and Motor Neuron Disease (Dr. Merchut)

### Neuropathy

#### 1. 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**. 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 begins 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.

#### 2. 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** 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**. 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 toximetabolic causes have axonal degeneration as the primary pathology**, with demyelination as a secondary or additional process.

### 3. 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 **electromyogram (EMG)**, which tests the electrical activity and function of nerves and muscles. EMG 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 EMG 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 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.

#### 4. Clinical polyneuropathy syndromes

One of the most rapidly progressive polyneuropathies is the **Guillain-Barre 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, areflexic 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 EMG 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. Despite even severe weakness, the vast majority of 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** (AIDS, leprosy (the latter more common outside the US)), **nutritional deficiencies** (B vitamins), and **toxins** (alcohol, lead, solvents, drugs).

### Myopathy

#### 1. 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, 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 **creatinine 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.

## 2. 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. EMG 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's (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 (Fig. 1). 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.

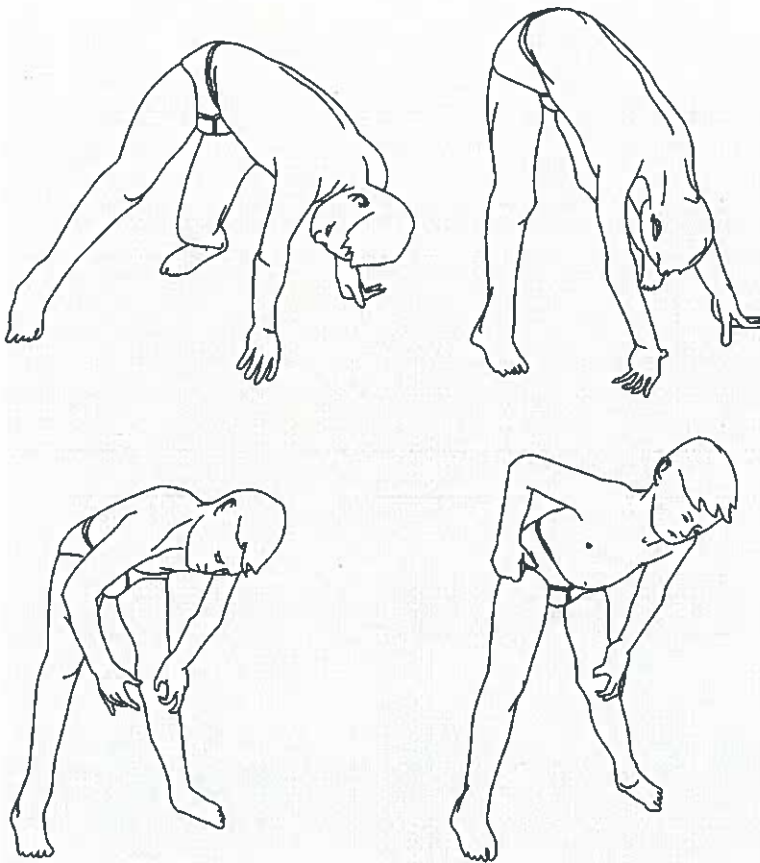


Fig. 1 Duchenne's muscular dystrophy. To stand, this boy must push or climb up his weakened lower trunk (Gower's maneuver).

Other hereditary myopathies have a pathogenesis which affects other body organs. **Myotonic dystrophy** type 1 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 1 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.

### **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 varies 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** 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, hyper-reflexia, 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)**, 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 hyper-reflexia 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, **EMG** 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. As ALS weakness progresses, patients and families must make choices about mechanical means of ventilation and nutrition.