Definition of Polyneuropathies

Polyneuropathies are defined as disorders of the peripheral and cranial nerves that are widespread and often symmetrical. They often present with both weakness and sensory loss in a “glove and stocking” fashion.

- **Myopathy** is a non-specific term used to refer to the disease of the skeletal muscle.
- **Dystrophy** refers to hereditary conditions which show dystrophic changes (increased connective tissue, fiber splitting) on biopsy. They are not
- Myositis implies an inflammatory process.

**Neuromuscular Junction**

Neuromuscular junction facilitates communication of neurons with muscle cells.

How does the neuromuscular junction work? Typically, a neuron (motor) will synapse with a muscle cell. The neuron is loaded with Acetylcholine in its presynaptic vesicles. Upon a nerve impulse entering the synaptic bouton, voltage-gated calcium channels are opened, causing the synaptic vesicles of ACh to move and fuse (with the help of the SNARE protein complex) with the bilipid membrane.

This releases acetylcholine into the synaptic cleft, whereby it diffuses across the synapse to its receptors on the myocyte. Here, the opening of calcium channels causing contraction of the myocyte via actin and myosin cross binding.

Many diseases occur at the neuromuscular junction and it is important to classify these as pre- or post-synaptic (botulinum toxin causes a presynaptic neuromuscular block whilst Myasthenic Gravis works postsynaptically).

**Etiology/Pathophysiology of Polyneuropathies**

Entrapment/compressive neuropathy
There is an extensive article on mononeuropathies which covers these topics in more detail. However, entrapments can cause polyneuropathies. Common entrapment/compressive neuropathies include:

- Median nerve at the wrist (carpal tunnel syndrome)
- Ulnar nerve at the elbow
- Radial nerve in the spiral groove
- Peroneal nerve at the fibular head
- Lateral cutaneous nerve of the thigh (meralgia paresthetica)

### Peripheral neuropathy

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<th>Relapsing</th>
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<td>Toxins</td>
<td></td>
<td>CIDP (chronic inflammatory demyelinating polyneuropathy)</td>
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<td>Uremia</td>
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Neuromuscular Junction and Myasthenia Gravis

Myasthenic Gravis causes polyneuropathies and can be a devastating disorder for those affected. It is an autoimmune disorder where antibodies have produced that bind to Acetylcholine receptors (ACh) and the neuromuscular junction. The antibodies result in an effective decrease in ACh binding in the neuromuscular junctions and lead to a number of severe symptoms.
A full history can be illuminating in the diagnosis of Myasthenia Gravis. Patients will often describe tell-tale symptoms; these include fluctuating ptosis (drooping of the eyelid). On questioning, they will say this is associated with tiredness and they also experience double vision when tired.

All other symptoms will also be worse when tired, and these can include bulbar symptoms like dysarthria and dysphagia. They will also experience trunk weakness. The symptoms can come on suddenly (and are not always associated with tiredness).

Functionally, these patients may have difficulty carrying out simple tasks like brushing their hair and walking upstairs. A crucial part of any history is asking about functional inability.

To officially diagnose Myasthenia Gravis, a number of investigations should be carried out. These can include the Tensilon test. In the test, acetylcholinesterase is given – this will rapidly improve all symptoms in the patient. Nowadays, however, the test has been superseded and is rarely used, although it is important to know of it for the USMLE step 2.

Other tests for Myasthenia Gravis include:

- **Ice test**: An ice pack is placed on the eye for 3-5 minutes. Ptosis will resolve in Myasthenic Gravis.
- **EMG**: Repetitive nerve stimulation causes a decremental response to stimulation.
- **AchR antibodies**: This is positive in about 80% of patients.
- **Chest CT**: To check for tumors of the epithelial cells of the thymus (thymoma). In patients with a thymoma, 85% antibodies against striated muscle.

Treatment of neuromuscular junction and Myasthenia Gravis

The first-line symptomatic treatment for patients suffering with Myasthenia Gravis are anticholinesterases. Examples include Pyridostigmine. Patients should also be put on an immunosuppressant long-term (e.g., Prednisolone). For short-term relief of symptoms, Plasmapheresis can be used (will only last a few days or a few weeks).

In patients with a thymoma, surgical resection of the tumor can often be a cure. Unfortunately, thymomas only make up a small portion of Myasthenic Gravis patients and most are incurable.
Prognosis of neuromuscular junction and Myasthenia Gravis

Patients with myasthenia gravis can lead normal life. Mortality rate is 3-4%. Mortality results from aspiration pneumonia, fall injuries, adverse effects of medication and respiratory failure.

Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome is an uncommon condition of the neuromuscular junction that is caused when auto-antibodies are raised to the presynaptic Ca2+ (Calcium) channels. This reduces the amount of Acetylcholine (ACh) release and thus muscular symptoms.

It is important to bear in mind the fact that Lambert-Eaton myasthenic syndrome is far more uncommon than other NMJ conditions like Myasthenia Gravis and, as such, should be lower down the list of differentials. Patients typically have proximal muscle weakness (think trunk), alongside various autonomic symptoms like a dry mouth or impotence. When patients consistently use a muscle, the symptoms should improve.

The syndrome can be paraneoplastic - that is to say, it is caused by a small cell lung cancer in 60% of cases. It can also be the result of autoimmune disease.

Differentiating Myasthenia Gravis from Lambert-Eaton myasthenic syndrome can be difficult at times, but there are a number of differences to look out for. Typically, these patients have gait issue before they have eye symptoms, whereas Myasthenia Gravis patients often present with a ptosis. The autonomic involvement is also a sign of Lambert-Eaton syndrome. Patients also have a diminished response to cholinesterases like Edrophonium.

A definitive diagnosis can be reached using EMG with repetitive stimulation. Unlike Myasthenia Gravis, patients have an increased (incremental) response to repetitive EMG firing. This is a key fact for the USMLE step 2 exam. In the vast majority of cases (90%), antibodies to the P/Q voltage-gated calcium channels are found.

In patients with small cell lung carcinoma – treat this. Resection of these tumors can halt symptoms.

Treatment of Lambert-Eaton myasthenic syndrome

In some patients, 3,4 Diaminopyridine is effective as treatment. AChE inhibitors will have little effect. Steroids and azathioprine can also be combined in treatment for immunosuppression in autoimmune cases.

Prognosis of Lambert-Eaton myasthenic syndrome

Prognosis of lambert–Eaton myasthenic syndrome (LEMS) is usually poor due to underlying malignancy. Quality of life is poor due to progressive weakness of muscles. LEMS does not affect vital muscles like in myasthenia gravis (MG). Maximum severity of weakness is attained within few months of onset of symptoms. In the absence of underlying malignancy, when it is caused by autoimmune disorder prognosis is determined by severity of symptoms and underlying autoimmune disease.
Botulinum Toxin

Botulinum is a neurotoxin produced by bacteria *Clostridium botulinum*.

Botulinum toxin is a protease that cleaves the SNARE proteins in the presynaptic terminals of the neuromuscular junction. These proteins regulate neurotransmitter release and, as such, ingestion of Botulinum toxin inhibits the release of Acetylcholine (ACh) from the neuromuscular junction.

Diagnosis of Botulinum toxin poisoning can be tricky, but a thorough history should be taken and you should make sure to ask if the patient cans their own foods or has prepared food with Botulinum toxin in (i.e., Pufferfish).

Patients usually have flaccid paralysis as the toxin inhibits the release of ACh. Without ACh, muscle contraction cannot take place and patients are unable to tense any muscles.

Causes of polyneuropathies:

- Immune mediated
- Metabolic
- Hereditary
- Toxic
- Infectious
Diagnosis of Polyneuropathies

For any polyneuropathies, a general process for diagnosis should be taken. The **history** (as with all of medicine) is vital and it is important to understand the time course of the presenting symptoms (as this grossly affects your differentials). Ask if there are any preceding events like **cancer** (some polyneuropathies are paraneoplastic). A history in all cases of suspected polyneuropathy should include **travel, alcohol/drugs/STDs and family history**.

The examination will often be obvious, but make sure to examine other systems that could be causing the polyneuropathy as a **secondary disease** (i.e., abdomen - **alcoholic liver disease**).

Investigations are dependent on history and examination findings, but, in general, **blood tests like FBC, LFT, U&E, TSH, B12** should be ordered. Also think of **autoimmune causes** and test for these. **Genetic testing** can be useful in suspected hereditary neuropathies. **Nerve conduction testing** can be useful in demyelinating diseases.

References


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