Polyneuropathies — Myasthenia Gravis, Peripheral Neuropathy, Entrapment and More

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This article deals with a number of polyneuropathies. It includes entrapment, compressive and peripheral neuropathy. It also includes information on the neuromuscular junction and myasthenic gravis, Lambert-Eaton Myasthenic syndrome and Botulinum toxin. It runs through each disease associated with these pathologies, their etiology/pathophysiology, diagnosis including history, examination and investigation and the treatment of diseases where appropriate.
Definition of Polyneuropathies

Polyneuropathies are defined as disorders of 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 nonspecific term used to refer to disease of the skeletal muscle.
- **Dystrophy** refers to hereditary conditions which show dystrophic changes.
(increased connective tissue, fiber splitting) on biopsy. They are not necessarily due to defects of the dystrophin gene.

- **Myositis** implies an inflammatory process.

**Neuromuscular Junction**

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, 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 postsynaptic** (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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### 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 are 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.
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 Ca\(^{2+}\) (Calcium) channels. This reduces the amount of Acetylcholine (ACh) release and thus muscular symptoms.

Botulinum toxin

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 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.

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.

Neuromuscular junction and Myasthenia Gravis

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, 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 up stairs. 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.

**Lambert-Eaton myasthenic syndrome**

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 of 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 time 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.

### Botulinum toxin

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. Puffer fish).


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

**Therapy of Polyneuropathies**

**Neuromuscular junction and Myasthenia Gravis**

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.

Lambert-Eaton myasthenic syndrome

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

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.

References


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