Charcot Marie Tooth Disease



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Pathophysiology

Hereditary Motor Sensory Neuropathy

Kid with Motor-body Sensor and Purple-wavy Neuron-extremities

Hereditary motor sensory neuropathies (HMSN) are progressive peripheral nerve disorders that are caused by dysfunction in Schwann cells due to a hereditary genetic cause. HMSN type I is called Charcot-Marie-Tooth disease (CMT) and is due to different mutations that lead to abnormal myelin function and structure. Other HMSN include Refsum disease (HMSN type IV) which is due to defects in alpha-oxidation in peroxisomes leading to the accumulation of phytanic acid.

Autosomal Dominant

Domino

CMT consist in a large group of genetic defects that results in a progressive peripheral neuropathy. CMT can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner. The most common is CMT type 1 which is inherited in an autosomal dominant pattern.

PMP22 Duplication

Pumpkins in (2) Tutus Duplicated

Most of the cases, up to 80%, of CMT are due to the duplication, or less commonly a point mutation, of the peripheral myelin protein 22 (PMP22) gene which is located on chromosome 17. Normally, the protein encoded by the PMP22 gene is a component of peripheral myelin proteins. In patients with PMP22 duplication, there is over expression of PMP22 protein and elevated PMP22 messenger RNA (mRNA).

Schwann Cell Dysfunction

Swan-cell with Chains

CMT is a spectrum of disorders caused by different mutations in genes that are normally expressed in Schwann cells which are the myelinating cells of the peripheral nervous system. Affected genes normally code for proteins involved in the normal structure and function of myelin and axons of peripheral nerves. There are multiple genes involved and most of them code for proteins involved in the structure and function of axons of peripheral nerves. The defect can lead to a demyelinating neuropathy and/or to axonal dysfunction. Therefore, in patients presenting with chronic motor and sensory polyneuropathy, CMT should be part of the differential diagnosis.

Clinical Features

Distal Muscle Weakness

Kid with Weak-distal-muscles

CMT disease is characterized by distal sensorimotor polyneuropathy that is usually symmetric. Early in the disease patients complain of frequent ankle sprains and difficulty running due to distal muscle weakness. As the disease progresses patients develop distal muscle weakness and atrophy. Sensory symptoms can also be present but are less prominent in comparison to motor symptoms. In general, if a patient presents with chronic motor symptoms and sensory polyneuropathy, CMT should be considered as part of the differential diagnosis. In the most common type of CMT, the symptoms present between the first and second decades of life.

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Foot Drop

Foot-drop

The most common initial clinical presentation is distal weakness and atrophy and a classical clinical finding is foot drop. In CMT1A, which is the most common form, the motor symptoms predominate and most patients present with clumsy walking although ambulation is usually preserved.

Calf Muscle Atrophy

Stork-legs

As the disease progresses distal calf muscle atrophy can occur and due to its appearance it is known as “stork leg deformity”. By this stage, patients have difficulty walking resulting in clumsy gait due to muscle weakness and sensory loss.

Scoliosis

Curved-spine and Skull

Another clinical finding in patients with advanced Charcot Marie Tooth disease is scoliosis. Scoliosis is a deformity of the spine that is characterized by lateral deflection and rotation of the spine.

Hammertoes

Hammer-toes

As the disease progresses some patients present with foot deformities including hammertoes and pes cavus. Hammertoes is a deformity consisting of the progressive proximal interphalangeal joint flexion deformity and compensatory hyperextension of the metatarsophalangeal and distal interphalangeal joints giving the characteristic hammertoe aspect.

Pes Cavus

High-arched feet

Pes cavus is a foot deformity consisting of the abnormally high plantar longitudinal arch. Pes cavus is a key presenting feature of CMT and if a patient has pes cavus in addition to motor symptoms and sensory neuropathy, CMT should be considered. If other features of CMT are found such as slowly progressive motor symptoms, hammertoes, and lack of positive sensory symptoms despite clear sensory involvement, the patient should be evaluated further for CMT.

Diagnosis

Onion-skin Appearance on Nerve Biopsy

Biopsy-needle and Onion

If nerve biopsy is performed, findings include demyelination affecting primarily large nerve fibers and onion bulbs. Onion bulbs correspond to repeated demyelination and de consequent remyelination which forms concentric arrays giving the characteristic onion peel appearance.

Electrodiagnostic Studies

Conduction-Cables and Electricity-shock

Patients being evaluated for neuropathy with slow progression of symptoms, foot deformities, sensory deficits, distal muscle atrophy, and a clear family history, should be further evaluated to rule out inherited causes of neuropathy. Electrodiagnostic studies are the next step and in most cases it is performed prior to genetic testing. Nerve conduction studies show decreased impulse conduction velocity in CMT disease. Needle electromyography is useful to confirm the presence of axonal neuropathy. If the clinical findings are suggestive and there is a family member with a known CMT mutation, then genetic testing can be performed immediately.

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