

## **Charcot-Marie-Tooth Disease (CMT); also referred to as Hereditary Motor And Sensory Neuropathy (HMSN) or Peroneal Muscular Atrophy**

### **What is CMT?**

Charcot-Marie-Tooth syndrome as it is widely known, is a group of hereditary conditions marked by slowly progressive muscle weakness and atrophy (wasting) in the feet, lower legs, hands and forearms. Many people also experience a mild loss of sensation in the limbs, fingers and toes. The weakness results from the degeneration of peripheral nerves (that connect the spinal cord to the muscles, joints and skin, carrying messages in both directions) rather than from a degenerative process in the muscle tissue itself.

### **What are the early symptoms?**

The first symptom of CMT is often difficulty in walking. This is caused by changes in the shape of the feet (high arches or very flat feet and flexed toes), ankle weakness, altered sensation and loss of movement in the foot and ankle. Typically, the knees have to be raised higher than normal to lift the feet off the ground. Some individuals have difficulty in maintaining balance while standing. Typical symptoms occurring in the upper limbs include difficulty picking up articles or dropping things due to weakness in the fingers, hands and wrists. Many people with CMT experience fatigue.

Charcot-Marie-Tooth disease (CMT), named for three physicians who first identified it in 1886, is also known as peroneal muscular atrophy because it primarily affects the peroneal muscles on the shin that allow one to pull up the foot. Although initially felt to be a single disorder, there is now thought to be a broad group of disorders that differ in clinical severity, genetic patterns of inheritance and changes noted in nerve biopsies. Collectively, this group of disorders is known as hereditary motor and sensory neuropathies (HMSN) and this is becoming the preferred term. However, the term Charcot-Marie-Tooth (CMT) disease is still very commonly used and generally refers to HMSN Type I.

### **What are the different types of HMSN?**

The most common forms of HMSN (Types I and II) differ chiefly in how function of peripheral nerves is altered.

**HMSN Type I:** Enlarged (hypertrophic) nerves and degeneration of the sheath of fatty material (myelin) that insulates many of the body's nerve fibres characterize this form of the disorder. This type is also known as the hypertrophic type. This degeneration of the insulating material gives rise to very slow conduction impulses in the nerves.

**HMSN Type II:** Also known as the neuronal form, it affects muscles of the lower limbs more than the small muscles of the hands that are predominately affected in Type I. There is a comparatively greater loss of muscle bulk below the knee, and weakness in the ankles and feet is also likely to be more severe. The nerve fibres (axons) rather than the myelin sheath are affected in this form of the disorder. Nerve signals in Type II are conducted faster than in Type I, but are often delivered incorrectly to their targets.

### How disabling is the disorder?

In most types of HMSN there is a limited disability, very slow progression of the disease and normal life expectancy. However, the severity of symptoms and rate of progression of the disorder can vary widely from person to person.

### How does the disorder progress?

As the disorder advances, muscles in the lower legs and sometimes lower third of the thighs become weaker and smaller in size (atrophic). This may further affect an individual's balance or ability to bend over. Hammer toes or clawed toes may develop.

Weakness accompanied by tremors may be experienced in the hands and forearms, usually in later stages. The intrinsic muscles of the hand can atrophy and the fingers can claw. Wrist drop can occur.

As a result, fine motor skills may become difficult. For some, numbness may be a problem in both hands and feet resulting in an increased risk for individuals affected by this disorder to injure themselves without realizing it. Painful sensations on the soles of the feet and palms may be a problem and sciatic nerve pain is not uncommon.

Some individuals may experience breathing difficulties resulting from weakness in the muscles of the diaphragm. Shortness of breath, dizziness, morning headaches, fatigue and pain in the rib area may result.

### What is the age of onset?

Because of the slow progression of the disorder, its onset is often difficult to determine. Generally, some changes in foot shape occur in late childhood or early adolescence in HMSN Type I. In HMSN Type II symptoms usually develop later, in early adult life or middle age.

### What is the current classification of the different types of HMSN?

The following table summarizes the most common genetic disorders associated with HMSN. HMSN Type I (classic CMT) is the most common of the disorders.

Pattern of Inheritance	Characteristics
<b>A. Autosomal Dominant HMSN I</b> (classic CMT I)	Variable degree of nerve hypertrophy, degeneration of the myelin sheath, at least 3 subtypes IA, IB, IC. Onset during late childhood or adolescence.
<b>A. Autosomal Dominant HMSN II</b>	Known as neuronal type, no nerve hypertrophy. Onset usually a little later than Type I.
<b>B. Autosomal Recessive HMSN III</b> (Dejerine Sottas Disease)	Onset in infancy or childhood, delay of motor milestones, nerve hypertrophy that is often severe.
<b>B. Autosomal Recessive HMSN IV</b>	Markedly slow motor nerve conduction velocity (NCV), other associated features.
<b>C. X-Linked Recessive X-Linked HMSN</b>	Similar to HMSN I but limited to males with no male-to-male transmission, females can be very mildly affected.

As mentioned previously, there is a great deal of variation between individuals in symptoms experienced and rate of progression, even among members of the same family. HMSN is not a life-threatening disorder.

## How is HMSN diagnosed?

Diagnosis is usually made through a detailed family and personal history and physical examination. This includes tests of muscle function and sensory responses. A laboratory test (nerve conduction velocity/electromyogram) measures the speed that impulses are carried down the peripheral nerves and the electrical activity of muscle cells. In addition, a complete family history is taken and if possible, careful physical examination of close relatives is pursued to determine if the individual's disorder is one that is inherited.

In some cases, nerve and muscle biopsies may be performed to enable the physician to confirm the diagnosis and specify the type, especially when symptoms are very mild or very severe and a family history of the disorder is not apparent. Both the electro-physiological nerve conduction velocity studies and muscle biopsy help to distinguish between the different forms of HMSN.

Also, by studying an individual's genetic material (DNA) isolated from a blood sample, diagnosis can sometimes be made. Recently, it has been discovered that approximately fifty percent of individuals with HMSN Type I (classic CMT Type I) have an extra copy of a small piece of genetic material within the CMT I gene. If this duplication is present, this confirms the diagnosis of CMT Type I. However, the absence of this duplication does not rule out CMT Type I or another form of HMSN. If this duplication is found in one individual, other family members can be similarly diagnosed with a simple blood test.

In addition, another gene on Chromosome 1 has been shown to have changes in it that appear to be causative of CMT Type IB. As more and more genes are isolated that are causing the various HMSN subtypes, the role of DNA testing in the diagnosis of HMSN will further expand.

## Is there any cure or treatment?

There is no known cure for HMSN. However, changes in foot shape, particularly high arches that are often very difficult to treat can be managed with carefully fitted shoes and proper foot care. In addition to good shoes, arch supports or AFO's (ankle-foot orthoses) within the shoes may be useful. Plastic splints may be used to prevent further foot drop. Surgery may be helpful in some cases, either to reduce the arch and the curling of the toes or to fuse together some of the foot bones. In some centers, tendon transfer is the surgery of choice to prevent changes in foot shape and the need for bone surgery.

## How does a person get HMSN?

HMSN Type I and II are inherited as autosomal dominant traits. This means that the altered, disorder-causing gene is passed on at the conception of a child by one parent of either gender who also has the disorder. That parent may have symptoms that are so mild they are unaware that they are also affected—however mildly—until their child is diagnosed. There is a fifty percent chance that a child born of either gender to a parent affected by the disorder, will inherit the gene that causes the disorder. Alternatively, there is a fifty percent chance the child will not have the disorder-causing gene.

In a small percentage of individuals where the trait is dominant, the altered gene arises spontaneously in that individual by a new change in their genetic material and neither parent appears to be affected.

There are also autosomal recessive and X-linked recessive forms of HMSN. In the autosomal recessive pattern of inheritance, a child who is affected must inherit a copy of the altered gene from both parents. Each parent is a carrier, which means they have one copy of the altered gene, but do not show any symptoms. Each child of either gender born to parents who are both carriers has a 25% chance being affected by the disorder and a 50% percent chance of being a carrier of the disorder-causing gene. In the X-linked recessive form, male children inherit the altered gene from their mother, who is a carrier. A male child born to a carrier mother has a 50% chance of being affected.

A regular program of moderate exercise can build up muscles and increase the mobility of joints. Active exercise and maintenance of a fitness regime help to sustain mobility.

Where numbness of the feet is a problem, regular washing, drying and inspection of the feet (for ulcerations, etc.) is important. Also, checking shoes to remove irritants such as stones and uneven edges is useful in keeping skin healthy.

Some people may find that use of a mobility aid such as a walker, scooter or wheelchair may be indicated. It is important to determine the aid, which is best for each person, and to ensure that seating is comfortable and correct.

For those experiencing symptoms in the hands, an Occupational Therapist can help in prescribing aides that help overcome obstacles. Fat pens, computers, lightweight utensils and clothing that is easy to put on and do up are examples of these aides.

A physician should carefully assess breathing difficulties for possible treatment. Avoidance of smoke is advisable.

For all clients with HMSN, regular visits to the doctor can help ensure that current concerns are treated and more serious obstacles avoided.

## What research is being done?

Recent advances in molecular genetics have extended knowledge and permitted major advances in understanding HMSN. Researchers have discovered a number of different genes that, when altered, can cause disorders of this type. Some examples of these genes are the PMP22 gene, found on chromosome 17 (Type 1A), and the Po gene, found on chromosome 1 (Type 1B). Each of these genes affects the myelin sheath, the covering around nerve fibers that provides insulation for the nerves. Scientists are gaining a greater understanding of exactly how the myelin sheath is made and how it works. Alterations in the genes that produce proteins vital to the makeup of myelin could prevent it from doing its job in a number of different ways.

Different changes on these same two genes are thought to be responsible for HMSN Type III and studies are underway with rats and mice having genetic alterations that are similar to this type of HMSN.

Scientists continue to explore the areas of nerve function and development, especially in relation to the myelin sheath, to gain more information about the pathological process in HMSN.

Based on these recent discoveries, other researchers are looking at the development of new treatment protocols. Their focus is on development of a drug that could positively affect a person's loss of function in the myelin sheath related to genetic alterations. Hopefully, drugs will be developed that would either halt or reverse the damage caused to peripheral nerve fibers and the myelin sheath that surrounds them. To this end, researchers have developed rat and mouse forms of HMSN Type 1A, and a mouse form for HMSN Type 1B.

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## How can I help?

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