

What is

Charcot-Marie-Tooth Disease

also known as Hereditary Motor & Sensory Neuropathy
or Peroneal Muscular Atrophy



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*"Working to support those who are affected by Charcot-Marie-Tooth Disease,
also known as Hereditary Motor and Sensory Neuropathy
or Peroneal Muscular Atrophy"*

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What is Charcot-Marie-Tooth Disease (CMT)

- ◆ Charcot-Marie-Tooth disease is also known as Hereditary Motor and Sensory Neuropathy and Peroneal Muscular Atrophy.
- ◆ is non life threatening
- ◆ is the most common inherited neurological disease.
- ◆ is very slowly progressive, causing deterioration of peripheral nerves which control sensory information and muscle function of the foot/lower leg and hand /forearm muscles.

An Explanation of all these Confusing Names

In 1886 two French neurologists (Charcot and Marie) and one English neurologist (Tooth) described a set of characteristic physical symptoms to which was later given their names - Charcot-Marie-Tooth disease (CMT).

Hereditary Motor and Sensory Neuropathy (HMSN) can be explained thus - Hereditary, because it is passed from generation to generation, Motor and Sensory because these are the two types of nerves which are affected and Neuropathy which describes any condition where nerves are involved. You will probably find that the majority of Health Care professionals you come into contact with will refer to the condition as HMSN.

Tooth discovered that one of the shin muscles, the Peroneus muscle, was one of the muscles which atrophies (wastes) as a result of the disease - hence Peroneal Muscular Atrophy (PMA) - now little used.

However, the story does not finish with CMT, PMA or HMSN. These all describe a group of conditions which all look the same, but are caused by different problems.

The Mechanics of CMT

The nervous system is effectively a two-way system. Messages from the brain travel via the upper motor neurones, down the spinal cord, through the lower motor neurones, such as the sciatic nerve in the leg, to the muscle. In the sensory system, the messages travel upward from the sensory input through the first sensory neurones, up the spinal cord, through to the brain. Peripheral nerves are in the limbs and are composed to two types of nerve fibre - motor nerves and sensory nerves. It is the peripheral nerves which are affected in CMT and thus there is a combination of motor symptoms (weakness/wasting) and sensory symptoms (numbness).

There are two main types of CMT. CMT Type 1 (Type 1A, Type 1B, Type 1C and Type 1X linked) involves a defect in the insulating substance that wraps around the peripheral nerves in the arms and legs, a substance called myelin, and is therefore known technically as "demyelinating neuropathy". Abnormal myelin means that the messages to and from the brain move very slowly.

In CMT Type 2, the fault lies in the core of the nerve, the axon. While the speed of signal transmission is nearly normal, there are other irregularities in the way the nerve functions.

The Types and Causes of CMT

There are a large number of genetic defects which cause all the different types of CMT.

Type 1A is caused, usually, by a duplication in a gene on chromosome 17. Instead of having two normal copies of the gene (one on each paired chromosome) there are three copies, two on one chromosome and one on the other. These genes produce a protein called PMP22, but just what this protein does in the myelin is not known. There are also some cases where there is only one gene on each chromosome, but one is defective. This causes exactly the same symptoms. Type 1A is detectable by a blood test, and therefore, gives a much more precise form of diagnosis. Previously diagnosis was done by nerve conduction studies, which measures speed of conduction of the nerves. In some cases a nerve biopsy was also used.

Type 1B is caused by a defect of a gene on chromosome 1. The gene produces a protein called myelin protein zero and is part of the myelin sheath. Again its role is not known.

Type 1C is also a demyelinating type, but its genetic origins are still unknown.

X-linked CMT is so called because the genetic defect which causes it lies on the X chromosome, one of the sex chromosomes. The gene produces a protein called connexin 32 which is involved in forming channels called gap junctions between cells. Just how this causes CMT is not yet known. This type is relatively common - 10-15% of all CMT cases.

The age of onset of all the variants of Type 1 is usually between 5 and 15, although it can be flexible in both directions.

Type 2 - the axonal type - is much rarer than the above types. However, the effects are very much as for Type 1. This generally develops later in childhood, between 10 and 20 or later. Type 2A is similar to Type 1 but the genetic defect is on chromosome 1. Type 2B is characterised by severe ulceration problems and the defect is on chromosome 3. Type 2C involves the vocal cords and diaphragm and its genetic origin is unknown. Type 2D, again is similar to Type 1 and its genetic defect is on chromosome 7.

Type 3 - Also called Dejerine Sottas Disease is now believed to be a particularly severe, childhood onset, variant of Type 1.

Type 4 is a group of types which can be axonal or demyelinating, and are mainly confined to certain ethnic groups.

Symptoms of CMT

All these types tend to produce fairly similar symptoms. The first sign noticed by doctors is slight difficulty in walking because of problems with picking up the feet. It is very common to have high arched feet but flat feet can also be a problem. Weakness of the hands occurs in most people, but not usually until later in life and the feet are always affected first. Some sensory loss is usual, which is not often troublesome, but the tendency to have cold feet is frequent. The reflexes are often lost, and is another pointer, often spotted early on by doctors.

These are not usually severely disabling disorders and often do not change a great deal after people have finished growing, although technically they are progressive. It is rare for people with CMT to lose the ability to walk, although walking aids such as walking sticks or orthoses may be needed. CMT varies enormously in severity, even within members of the same family.

Much more rare symptoms can be - severe early onset, spinal curvature, hip problems, speech and swallowing difficulties, diaphragm weakness, and tremors. We stress, however, these are MUCH rarer.

It is also possible to have the genetic defects which cause the various types of CMT, yet display no symptoms at all. However, there would still be a risk to the following generations.

The Genetics of CMT

It is important to know which type you have, so that you know the inheritance implications.

The different types are inherited in different ways, so advice given in genetic counselling will vary depending on the type of CMT and its mode of inheritance. We all inherit genes in pairs, one from each of our parents.

There are three inheritance patterns for CMT.

Autosomal Dominant - Type 1A, Type 1B and Type 2

The most common form of inheritance is autosomal dominant, whereby the affected person has one normal and one abnormal gene in the relevant pair and each child of an affected parent has a 50/50 chance of being affected. People of either sex can have the condition.

For example:

Affected parent <-----> unaffected parent

With each pregnancy, this couple have a 50% chance of having an affected child (of either sex).

- An unaffected child cannot pass on CMT to their children, since they do not carry the abnormal gene.
- An affected child has the same 50% chance of having an affected child as it's parents.

Autosomal Recessive - Type 4

In some families with Type 1 and Type 2 and in all families with Type 4, the inheritance is autosomal recessive. In this case, both the parents have to be "carriers" of the faulty gene before the child will be affected. Neither parent will have any symptoms, but the child will receive a double dose of the defective gene and therefore the condition will develop. Each child has a 1 in 4 chance of being affected and it can affect both males and females.

For example:

Carrier parent <-----> Carrier parent

With each pregnancy, these parents have a 25% chance of having an affected child (of either sex), a 25% chance of having an unaffected child (of either sex), and a 50% chance of having a carrier child (of either sex).

- The affected child will only pass CMT on to children if they are unfortunate enough to have a partner who is also a carrier of this type of CMT.
- The unaffected child cannot pass on CMT to their children, since they do not have the abnormal gene.
- The carrier child (who is also unaffected) has a 50% chance of having a child who is a carrier.

At present, there is no method of detecting carriers of this type of inheritance.

X-Linked - Type 1X

The third form of inheritance is called X-linked. In this case, the faulty gene is carried on one of the sex chromosomes which determine the sex of the child. Females are XX and males are XY. In this form of CMT, the disease is inherited by boys from their mothers who are carriers. The mother will either have no symptoms at all, or be very mildly affected. Each of the sons will have a 50% chance of having CMT, which is likely to be more severe than his mother, and each of the daughters will have a 50% chance of being a carrier.

For example:

Carrier mother (who could be slightly affected) <-----> unaffected father

With each pregnancy every son born to these parents has a 50% chance of having CMT more severely than his mother and every daughter has a 50% chance of being a carrier and could be mildly affected.

- Any affected son cannot pass CMT to his sons but all his daughters will be carriers.
- Carrier daughters have a 50% chance of passing CMT onto their sons.
- Any unaffected children cannot pass CMT onto their children, nor is there a risk of them being carriers, since they don't carry the affected gene.

New Mutations

It is possible for Type 1 CMT to develop spontaneously and this will become autosomal dominant - ie there will be a 50/50 chance of this mutation being passed onto subsequent offspring.