



Charcot-Marie-Tooth disease (CMT)

Overview

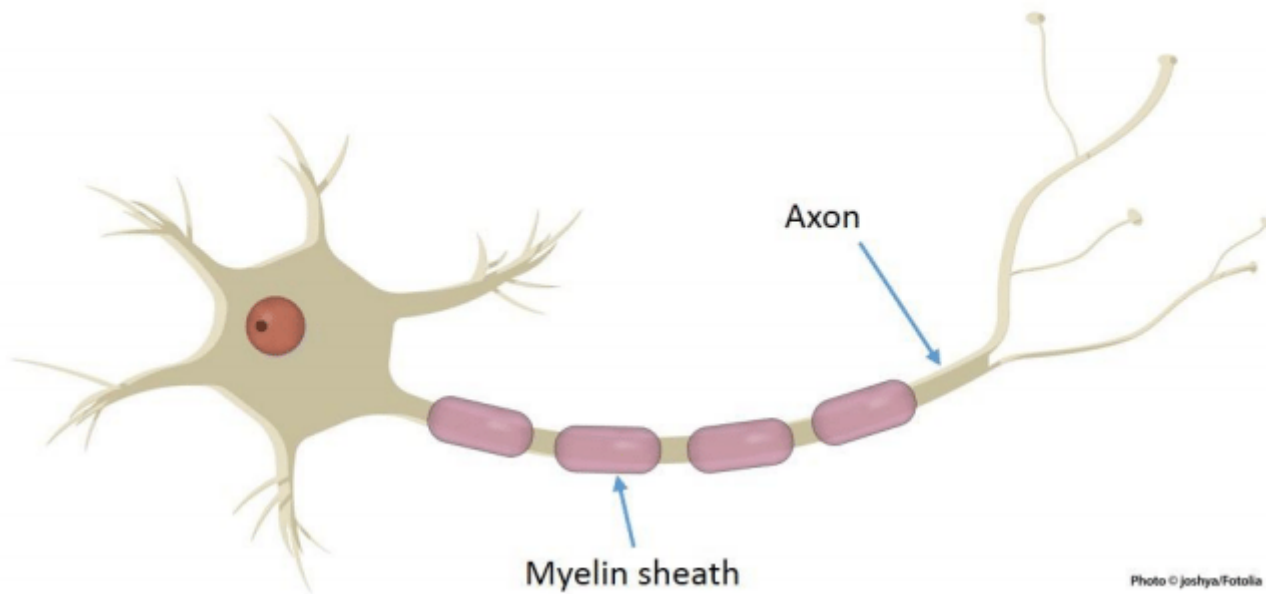
CMT is a group of genetic conditions affecting the peripheral nerves, which connect the brain and spinal cord to the rest of the body. It is commonly referred to as hereditary motor and sensory neuropathy (HMSN), which refers to its two primary features: it is hereditary and affects the function of the motor and sensory peripheral nerves.

The motor nerves carry messages from the brain and spinal cord to our muscles, telling them to contract. The sensory nerves convert specific external stimuli, such as touch and pain, into signals that are transmitted back to the brain. CMT causes the motor and sensory nerves to become damaged and eventually die. This leads to weakness and wasting of the muscles below the knees and often those of the hands. It can also cause numbness or loss of feeling in the hands and feet (the 'sensory' component).

CMT is also referred to as peroneal muscular atrophy, as the peroneal muscles on the outer side of the calves are particularly affected. Other names include Dejerine-Sottas disease and hereditary hypertrophic neuropathy. CMT is the favoured and most commonly-used name. There are two main types of CMT – type 1 and type 2. They are classified according to exactly which part of the nerve is damaged. If you think of a nerve as an electrical cable, the part of the nerve called the axon is the metal wire that conducts the electrical signal (see figure below). Around the axon is a protective myelin sheath – the plastic insulation you'd find around an electrical cable. In CMT type 1, it is the myelin sheath that becomes damaged and in type 2 it is the axon itself that is damaged. This nerve damage results in muscle weakness and wasting, as well as loss of sensation.

These two main types of CMT are further divided into sub-types, depending on how they are inherited and the gene that is involved.

Nerve cell



Symptoms

In the more common types of CMT, the first signs usually appear in the first 10 years of life. In other types, it may not be until very much later, even into middle age. Parents may well notice the first symptom, which is often a slight difficulty in walking because of problems with picking up the feet.

Many people with CMT, particularly CMT type 1, have high arched feet (known as pes cavus). This may be obvious from a very early age, and tends to become particularly noticeable at the time of the growth spurt associated with puberty. Some people have weakness in their hands, but this does not usually cause symptoms until after the age of 20.

People can have numbness in their feet and hands (they usually notice it in the feet first), which is not often troublesome. Having cold feet is quite common too. Very rarely, people can experience severe numbness, which means you can easily injure or hurt yourself without knowing it. For example, you may develop ulcers on your feet if your shoes don't fit well, or burn your hands on hot cups, and so on.

Although pain is a common experience for people with CMT, neuropathic pain (nerve pain which has specific characteristics) is less common. What can be more common is pain from secondary effects on the joints or from foot deformities, or muscle cramps. People may lose the reflexes (such as the knee jerk), which doesn't cause any trouble, but doctors will often notice this early on. A few people with CMT 1 have shakiness of the hands (tremor). The combination of tremor and CMT is sometimes referred to as the Roussy-Levy syndrome.

The types of CMT which run through the generations in families are not usually severely disabling and are very slowly progressive. It is unusual for people with CMT to lose the ability to walk, although some people – especially when they are older – need to use a stick or other walking aids. It is important to stress that the condition often varies enormously in severity, even among

members of the same family. Ten to 20 percent of people with the condition have no symptoms at all, however examination or electrical testing may show that they do have the condition.

Causes

Over the last two decades, researchers have identified more than 80 genes in which mutations are known to cause CMT.

These mutations usually affect the production of a particular protein in the peripheral nerves, either causing the protein to be faulty or not produced at all. How this then leads to damage of the peripheral nerves is not well understood for all types of CMT, however, many researchers around the world are looking into this. The most common sub-type of CMT is CMT 1A. It is usually caused by the duplication of a gene on chromosome number 17.

This gene carries the instructions for a protein found in myelin, called peripheral myelin protein 22 (PMP-22). Individuals with this condition have an extra copy of PMP-22 (three copies instead of the usual two) because they have an extra copy of a small part of chromosome 17 containing the PMP-22 gene. Although this mutation, commonly called the chromosome 17 duplication, is usually inherited in an autosomal dominant manner, it has been found in some individuals with healthy parents and thus represents a new mutation. More rarely, people with CMT1A have a change in, rather than a duplication of, the PMP-22 gene.

How is CMT inherited?

There are different inheritance patterns for different types of CMT. Most sub-types of CMT type 1 are inherited in an autosomal dominant manner. This means that you only need to inherit the faulty gene from one parent to have the condition. CMT X1 is the only exception in the type 1 category – it has X-linked inheritance, which means it is determined by a gene carried on the X chromosome (one of the sex chromosomes).

As males have only one X chromosome, and females have two, males tend to be much more severely affected by CMT X1 than females. Although most sub-types of CMT type 2 are autosomal dominant, there are a few rare sub-types that are inherited in an autosomal recessive manner. This means that you need to inherit the faulty gene from both parents to have the condition. For more explanation on the different patterns of inheritance, please see our [Inheritance factsheet](#).

Diagnosis

It is important to determine exactly what type of CMT someone has, so that they can receive the correct care and understand the inheritance pattern too (as discussed in the previous section).

This can be achieved through careful examination, taking a family history, electrical tests and genetic studies on blood samples. This sort of assessment can also distinguish CMT from other non-genetic causes of neuropathy. The initial and most important tools in diagnosing CMT are electrical tests (called nerve conduction studies), which measure the patterns of electrical activity present in the nerves and record how quickly and how well electrical impulses travel along them. Children with CMT 1A will show the typical electrical abnormality from about the age of five.

Genetic tests are usually performed on a blood sample. The tests aim to identify which faulty gene is causing a condition and the precise nature of the genetic fault, in other words, the mutation. There are several different types of mutation, which are named for their effect on the DNA. For instance, a 'deletion mutation' is caused when some of the DNA is deleted and 'duplications' occur when part of the DNA is repeated. Testing for the chromosome 17 duplication, which causes most cases of CMT 1A, is widely available in most regional genetic laboratories. Some genetic laboratories or researchers have recently begun to use new sophisticated techniques to identify mutations in genes. To find out more about testing for a specific sub-type of CMT, contact your local genetic counselling centre. They may need to do a detailed assessment, including blood and electrical tests, of your close relatives.

If you have any questions, please contact us on 020 7803 4800 or info@musculardystrophyuk.org. Occasionally, members of a family with CMT, who don't have signs of the condition or electrical abnormalities, may request a genetic test to see if they are likely to develop the condition in the future (predictive testing). In unaffected children, it is advised to wait until they are adults and can make their own decisions about testing.

Treatment

There is no specific treatment at present for CMT, although there is much research taking place. There are, however, other ways to manage your symptoms, such as issues with your feet, to improve your quality of life.

One of the most common symptoms of CMT is high arched feet, which makes it difficult to find well-fitting shoes with good support. Arch supports or other devices, such as good insoles, can be helpful to correct, support and maintain the foot position.

For people who have quite a lot of weakness in their leg muscles, splints or Ankle Foot Orthoses (AFOs) can often be helpful. They reduce the tendency of the foot to drop, and prevent tripping and falls. There are always new types of splint on the market, and you can discuss options with your physiotherapist. For those who experience numbness in their feet, it is helpful to take extra care of the feet. Wash and dry them carefully, and inspect the skin for small ulcers, which you might not feel. Shake out the inside of your shoes to remove small stones, and so on, and check for irregularities that could damage your skin.

Annual appointments with a neurologist or a paediatrician will help children and teenagers with CMT avoid severe problems with the feet developing. Surgery may be helpful if you have very high arched feet; either to reduce the arch and the often associated curling of the toes, or to fuse together some of the foot bones. After procedures of this sort, and any other operation, try to keep active and not spend too much time in bed, as you may notice increased difficulties in walking afterwards. Active exercise and maintaining fitness will also help to maintain mobility.

Studies have shown the benefits of exercise in keeping the less affected muscles strong and improving stamina. Exercise can also help to improve balance and stretch out tight muscles, such as the calf muscles. A small number of people with CMT may have curvature of the spine, known as scoliosis. It doesn't usually need surgery, but the few severe cases may need to consider it. Some people may also have hip joint problems that may require surgery.

Medication and anaesthetic precautions

Make sure that any medical practitioners are aware of a diagnosis of CMT when they are prescribing new medication. In theory, there is a slight chance that some drugs and medication may have an adverse effect on people with CMT. Vincristine is the only drug that is known to carry the risk of acute worsening of CMT1A. This drug is used in chemotherapy (treatment for tumours) and patients with genetically confirmed CMT1A should not be prescribed it. As a general rule, make sure that any doctor who is about to treat you knows you have CMT.

Anaesthetics should not cause any particular problems, providing the correct protocol for people with neuromuscular conditions is followed. Spinal or epidural anaesthesia have been reported as successful techniques. Make sure the anaesthetist knows about your condition before any operation, as your respiratory function might need to be checked.

Research into CMT

As you'll have read, over 80 genes have been identified as linked with CMT, and this is likely to increase further in future. Scientists are trying to understand more about the underlying biology of CMT and how this leads to symptoms. This knowledge is important in order to develop effective treatments. Find out the [latest news on CMT research](#).

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The friendly staff in the care and support team at the Muscular Dystrophy UK's London office are available on 0800 652 6352 or info@muscular dystrophyuk.org.

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