

## Charcot-Marie-Tooth Disease (CMT)

Sometimes known as Hereditary Motor and Sensory neuropathy (HMSN) or Peroneal Muscular Atrophy (PMA)

### What is Charcot-Marie-Tooth disease?

Charcot-Marie-Tooth disease is named after the three neurologists who first described the condition in 1886. Many different names have been used to describe CMT but the other commonly used name is hereditary motor and sensory neuropathy (HMSN). This is an accurate term as it refers to the two primary features of this condition i.e the condition is hereditary and affects the motor and sensory peripheral nerves. CMT or HMSN therefore is used to describe a group of conditions that give rise to weakness and wasting of the muscles below the knees and often those of the hands. Many affected people also have loss of feeling in the hands and feet, and this is the 'sensory' component. The term neuropathy refers to the fact that it is the peripheral nerves (which connect the spinal cord to the muscles, joints and skin, carrying messages in both directions), which do not function normally. As the name implies, these are inherited disorders.

CMT is also referred to as peroneal muscular atrophy, because the peroneal muscles on the outer side of the calves are particularly affected. Other names include Dejerine-Sottas disease and hereditary hypertrophic neuropathy. The term CMT is now the favoured term and is the term most commonly used in the literature.

CMT does not describe a single disorder, but a group of conditions that are superficially similar. It is important to determine exactly what kind of CMT someone has, and this can be achieved by careful examination, taking a family history, electrical tests (nerve conduction studies), and genetic studies on blood samples. This sort of assessment also serves to distinguish CMT from other non-genetic causes of neuropathy, and this is particularly important in people who do not have affected relatives.

### The different types of CMT

Peripheral nerves can be thought of as being electrical cables: the fibres (like wires) run down the middle and are wrapped in insulating material (myelin).

If the myelin is damaged the nerve impulses tend to be conducted more slowly than usual. If the fibres (also called axons) are damaged, the speed of conduction is normal but the size of the signal is reduced.

These changes can be detected by electrical tests. Traditionally, the commonest forms of CMT have been divided into two types: in type 1 the damage is to the myelin resulting in slow conduction, and this is referred to as the demyelinating type of CMT, whereas in type 2 it is the nerve fibres that are at fault and the term axonal type CMT is used.

Although major advances have been made in the last decade in the identification of the genes responsible for CMT, not all of the genes associated with CMT have yet been identified. This means that the electrical test (nerve conduction studies) is still often very useful in making the diagnosis. An exception is when there is a clear family history of autosomal dominant inheritance (see below), when DNA testing for the commonest form of CMT (type 1A) might be performed as a first investigation. Although the electrical tests are usually clearcut, allowing a diagnosis of CMT type 1 or CMT type 2, in some cases it may be difficult to decide from the electrical test which type of CMT a patient has and the term intermediate CMT is used. Although this can be confusing for patients it is useful for doctors in deciding which genes to screen. In the future, when all the causative genes are identified, a comprehensive classification of CMT will be available but in view of the fact that there are likely to be numerous genes involved it is probable that electrical tests will remain important in the initial assessment of patients.

Previously, the term HMSN III was applied to patients with a particularly severe form of HMSN starting in very early life. HMSN III is also called Dejerine Sottas Disease (DSD) and Congenital hypomyelinating neuropathy (CHN) and both these terms are commonly used clinically. HMSN III was thought to be inherited in an autosomal recessive pattern, unlike the autosomal dominant pattern of inheritance of the common types of CMT types 1 and 2 (see below). We now know that HMSN III is usually associated with a defect in the genes that cause CMT type I and that most cases are a result of a new mutation in the gene, which explains why neither parent was affected. Therefore the term HMSN III is no longer commonly used, having been replaced by the terms CMT 1, DSD and CHN. Occasionally DSD and CHN can be inherited in an autosomal recessive manner.

There are other more complex forms of CMT in which the neuropathy is combined with other features such as deafness, visual problems, vocal cord paralysis and breathing difficulties but these are all very rare.

### **How does CMT affect people?**

The first evidence of CMT is usually between the ages of 5 and 15 but sometimes may not be until very much later, even into middle-age. Usually the first symptom is slight difficulty in walking because of problems with picking up the feet, and this may well be noted by parents first. Many people, particularly those with CMT type I, have high arched feet (referred to as pes cavus) and this may be obvious from a very early age. It tends to become particularly noticeable at the time of the growth spurt associated with puberty. Weakness of the hands occurs in some people, but this does not usually cause symptoms until after the age of 20.

Patients can experience numbness of the feet and hands (usually noticed in the feet first) which is not often troublesome, but the tendency to have cold feet is frequent. Very rarely the numbness can be severe, and it is then easy for affected individuals to injure themselves without knowing it; painless ulcers of the feet may develop as a result of poorly fitting shoes, or burns on the hand from hot cups etc. Pain is not a common feature of CMT and if present may be due to secondary effects on the joints or muscles. The reflexes (such as the knee jerk) are commonly lost. This does not cause any trouble for the individual, but is often noted early on by doctors. A few people with CMT 1 have shakiness of the hands (tremor) and the combination of tremor and CMT is

sometimes referred to as the Roussy-Levy Syndrome. Mild curvature of the spine (scoliosis) occurs in some people and tends to be more severe in those with early onset of limb problems.

The types of CMT which run through the generations in families (see section on dominant inheritance) are not usually severely disabling disorders and often do not change a great deal after people have finished growing. It is unusual for people with CMT to lose the ability to walk, although some older people need a stick or other walking aids. It is important to stress that the disorder often varies enormously in severity, even in members of the same family, and 10 to 20% of affected individuals have no symptoms at all but are found to have evidence of the condition on examination or using electrical tests.

### **How is CMT inherited?**

The commonest forms of CMT are inherited in a way that is referred to as autosomal dominant (AD). This type of inheritance is the most common type in CMT 1 and CMT 2. We all have two copies of every gene and in AD inheritance, the affected person has one abnormal gene and one normal gene. Each child will only inherit one gene from an affected parent (the other gene will come from the other parent) and therefore each child of an affected parent has a 50% chance of inheriting the abnormal gene and being affected. People of either sex can have the condition.

However in occasional families with CMT 1 and CMT 2 the inheritance is autosomal recessive (AR). In AR inheritance a person needs two abnormal copies of the gene to be affected unlike AD inheritance where the person only needs one copy of the abnormal gene to be affected (see above). AR inheritance is only seen if both parents are 'carriers' of the faulty gene but these parents do not themselves have any symptoms. Both parents therefore have one abnormal and one normal copy of the gene. The condition develops only if a child inherits the abnormal gene in a double dose, i.e. one from each parent. Each child of such parents has a 25% chance of inheriting an abnormal copy from both parents (double dose) and being affected. Each child of such parents will have a 50% chance of inheriting one abnormal copy of the gene from either parent and be a "carrier" of the condition and each child will have a 25% chance of inheriting two normal genes (one from each parent). Males and females can be affected. Many people with autosomal recessive CMT do not have affected relatives as each child has only a 1 in 4 chance of being affected and most families are quite small. It is therefore common for only one child to be affected.

In some families, CMT is caused by an X-linked gene (X-linked inheritance) which is carried on the X chromosome, one of the so-called sex chromosomes which determine the sex of the child (females are XX, males are XY). The result is that boys inherit the disease from their mothers who are known as carriers. Carriers may show no sign of disease, although sometimes they are mildly affected, but each of their sons has a 50% chance of having CMT and each of their daughters has a 50% chance of being a carrier. Affected males cannot transmit the disease to their sons. In these families therefore, males are more severely affected than females and males cannot pass on the disease to their sons.

It is very important to establish exactly what type of CMT someone has, and to investigate family members, as advice given in genetic counselling will vary depending on the type of CMT and its mode of inheritance. This may require detailed family investigations, as some mildly affected family members may not have any symptoms.

### **What is the cause of CMT?**

There have been major advances in the last decade in the identification of the causative genes for CMT. To date there have been 16 causative genes identified and at least 8 other loci (location on a chromosome where a causative gene is but where the causative gene has not been identified). Most of these genes have been identified for CMT 1 and at the moment patients with CMT are more likely to have the causative gene identified if they have CMT 1 rather than CMT 2.

In most families with dominantly inherited CMT I, the abnormal gene is located on chromosome number 17. This variety of CMT is called CMT 1A and is due to abnormalities in a protein found in myelin called peripheral myelin protein 22 (PMP-22). The commonest genetic abnormality of the PMP-22 gene in patients with CMT 1A is unusual; affected people have an extra copy of the gene (3 copies) because they have an extra copy of a small part of chromosome 17 containing the PMP-22 gene. Although this genetic abnormality, commonly called the chromosome 17 duplication, is usually inherited in an autosomal dominant manner, it has been found in some individuals with normal parents (and thus represents a new mutation). Rarely patients with CMT 1A have a different abnormality (a mutation) of the PMP-22 gene.

About three-quarters of patients with CMT I have type 1A. The second commonest form of CMT 1 is CMT 1X, where patients have a mutation of the connexin 32 gene on the X chromosome. In recent years this form of CMT has been diagnosed more commonly as doctors recognise X-linked inheritance in families.

The third well recognised type of AD CMT 1 is CMT 1B where patients have a mutation in a gene (myelin protein zero, P0) on chromosome 1.

Recently mutations in five genes have been described in autosomal dominant CMT 2. Unlike CMT 1, there is no one gene that affects most patients and it has yet to be determined how common mutations in these five genes will be as a cause of CMT 2. Interestingly, occasionally mutations in myelin protein zero (P0), which usually causes CMT 1B, can cause CMT 2. The exact reason for this is not known yet.

Mutations have now been described in seven genes causing autosomal recessive CMT 1 and CMT 2 (excluding the rare cases of DSD and CHN that can be autosomal recessive). Most of these have been described very recently and it remains to be seen how commonly mutations in these genes will cause AR CMT 1 and AR CMT 2.

It is important for patients with CMT to know which genes are currently available for testing in the UK. Testing for the chromosome 17 duplication referred to above, which causes most cases of CMT1A, is widely available in most regional genetic laboratories. Testing is also easily obtained for CMT 1X (connexin 32), PMP-22 mutations (CMT 1A) and P0 (CMT1B and CMT 2). Testing for

all of the other AD CMT 2 genes and all of the AR CMT 1 and AR CMT 2 genes is not yet routinely available but for individual genes testing may be available on a research basis.

### **Problems and management**

There is no specific treatment at present for the underlying genetic defect in CMT even in those patients in whom a genetic diagnosis has been made although there are many groups researching this area. This does not mean that patients with CMT cannot be treated or helped in many other ways. It is very important that problems patients experience such as foot problems are addressed appropriately and this may greatly improve a patient's quality of life. Accurate genetic diagnosis and genetic counselling is the other area of management in which there has been rapid development in recent years.

One of the most common problems in CMT is difficulty in getting well fitting shoes because of the arched feet. It is important to wear shoes with good support, and arch supports or other devices within the shoes may be needed. In people who have quite a lot of weakness of the leg muscles, splints are often very helpful to reduce the tendency of the foot to drop. New types of splints are continually being developed and patients should discuss the options with their physiotherapist. Ideally children and teenagers with CMT should be seen annually by a neurologist or a paediatrician to ensure that severe problems with the feet do not develop. Surgery may be helpful for very highly arched feet, either to reduce the arch and the curling of the toes which often goes with it, or to fuse together some of the foot bones. After procedures of this sort, and any other operation, it is essential to minimise periods spent in bed, as increased difficulties in walking are often noticed afterwards. Just as rest may enhance difficulty in walking, active exercise and maintaining fitness help to maintain mobility. Surgery is not usually needed for scoliosis but may have to be considered in the very few cases in which this is severe. In those with a lot of numbness of the feet, it is important to take great care of the feet, washing and drying them carefully, and inspecting the skin for small ulcers. The inside of the shoes should be shaken out to remove small stones etc., and the insides felt for irregularities that could damage the skin.

Accurate genetic counselling is one of the mainstays of management and typically involves detailed assessment, including blood and electrical tests of close relatives. Despite the major advances in understanding the genetic abnormalities in CMT, the electrical studies remain the initial and most important tool in the diagnosis of most patients. In CMT 1A, affected children will show the typical electrical abnormality from about the age of 5 years. Once a genetic diagnosis is made in a patient with CMT, the blood test can then be used to diagnose other affected members of a family. Occasionally members of a family with CMT without signs of the disease or electrical abnormalities request a genetic test to see if they are likely to develop the disease in the future (predictive testing). This is usually not done in unaffected children, the preference being to wait until they are adult and can make their own decision about testing. The interpretation of predictive testing can be difficult in rare causes of CMT as the information is not always available about whether having an abnormal gene means that a person will always develop the disease. Predictive testing needs to be discussed on an individual basis for each patient. In some families blood tests can be used for pre-natal diagnosis by analysing a small sample of the placenta taken at about 10 weeks of pregnancy. Couples wishing to consider this option should make enquiries through their regional clinical genetics centre before embarking on a pregnancy.

### **Contacts**

The CMT Support Group offers support and encouragement to families and individuals with CMT. For further details please contact:

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MC04

Published: 01/2004

Updated: 04/08

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