Charcot-Marie-Tooth UK

What is CMT?

Together we are Stronger

Published by Charcot-Marie-Tooth UK

Charcot-Marie-Tooth Disease

Charcot-Marie-Tooth Disease (CMT) is a condition that damages your peripheral nerves. These nerves are responsible for passing on commands from your brain to your muscles (motor nerves) and for passing information to the brain about sensations, such as pain, heat, cold and touch (sensory nerves).

Because of the nerve damage, people with CMT may find that some of their muscles become slowly weaker over the years, particularly in their feet and hands. And some people find that their sense of feeling becomes duller, or numb, in the same areas.

In the UK, some 25,000 people are thought to have CMT (approx 1:2500) making it the most common inherited neurological condition.

Other key points about CMT are that it:

- Is hardly ever life threatening, but often becomes slowly worse over the years – ie, it is progressive
- affects people very differently, even in the same family
- can cause the muscles in the foot, lower leg, hand and forearm to get weaker (waste)
- can cause foot drop walking gait, foot bone abnormalities (eg high arches and hammer toes), problems with hand function, balance problems, occasional lower leg and forearm muscle cramping, and loss of some normal reflexes
- may cause long-term pain and tiredness (fatigue)
- is usually passed on from parent to child
- affects all ethnic groups throughout the world

What does CMT stand for?

CMT is an acronym for Charcot-Marie-Tooth, the surnames of the three doctors that first described CMT in 1886: Frenchmen Jean-Martin Charcot and Pierre Marie; and Howard Henry Tooth from the UK.

CMT has many other names, the most common being:

Hereditary motor and sensory neuropathy (HMSN) – so called because it is passed on through families (hereditary) and affects both the motor and sensory nerves (neuropathy).

Peroneal muscular atrophy (PMA) – so called because one of the muscles that is often first affected, becoming weaker and wasted (atrophied) is called the peroneus muscle, found in the shin.

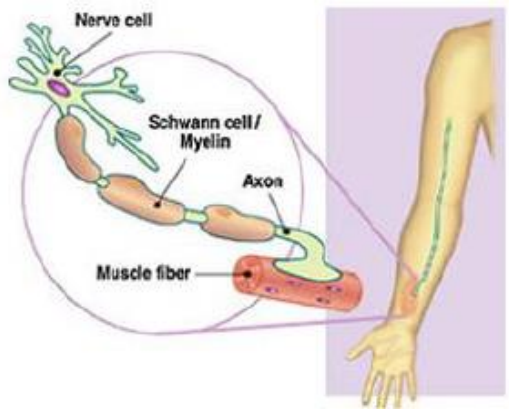
Today the term CMT is the most commonly used, although HMSN is still used in some medical literature.

What causes CMT?

CMT is caused by a genetic fault (mutation) that leads to damage of the nerves in your legs or arms.

In order for you to move with speed and precision, messages have to be relayed between your brain and the rest of your body within a fraction of a second. These messages are relayed through your nerves.

For example, if you want to move your leg, an electrical message is sent from your brain, via the spinal cord, to the muscles in your leg along a motor nerve. If you cut or burn your leg, you feel it because an electrical signal is sent from the affected area, up the sensory nerves, via the spinal cord, to your brain.



The nerves in your arms and legs, called peripheral nerves, can be compared to electrical cables. The central 'wire' is known as the axon and the 'plastic outer' is called the myelin sheath.

Axons transmit the electrical signals to and from the brain, and myelin sheath acts as insulation, speeding up the signal and nourishing the central axon. Some forms of CMT affect the axon – making the signal to and from the brain weaker and less efficient. Other forms of CMT affect the myelin sheath, slowing down the signal. But even if the myelin is the problem, until there is damage to the axon there will be no symptoms of CMT.

Without an intact axon and myelin sheath, your nerves are unable to activate target muscles or relay sensory information from your limbs back to the brain.

As at summer 2015, 82 genes have been found to cause different types of CMT. Each one of these genes is responsible for making particular proteins that are essential to the axon or myelin sheaths.

The different types of CMT

There are two main types of CMT:

1. **Demyelinating** (CMT1) – this form of CMT affects the myelin sheath that insulates the central axon.

2. **Axonal** (CMT2) – this form of CMT affects the central axon.

There are two other variations of CMT1 and CMT2, known as:

CMTX

DI-CMT

You may have heard of other types of CMT - CMT4 for example. Because of our better understanding of the genetic causes of CMT, we now know that all of these 'different' types are in fact simply variations of the two main types – demyelinating and axonal. Type 4 is still used to classify the Autosomal Recessive types of CMT, but these can still be either demyelinating or axonal.

Demyelinating CMT (CMT1)

CMT1 is the most common form of CMT (six out of ten people with CMT will have CMT1A), affecting the nerve's insulating myelin sheath. CMT 1A is caused by a duplication on chromosome 17 – instead of the usual two copies of the relevant gene, there are three. This type can be detected by a blood test that is now widely available in the UK.

People with CMT1 will usually notice symptoms developing in childhood or adolescence (usually between the ages of five and 15. NB .Age of onset can be earlier or sometimes later than stated)

Some forms of CMT1 have an earlier age of onset and these forms used to be called HMSN3 in the old classification. Two of these forms are called Dejerine Sottas disease (DSD) and Congenital Hypomyelinating Neuropathy (CHN).

Axonal CMT (CMT2)

CMT2 is not as common as CMT1, but has similar symptoms. Rather than damaging the nerves' insulating myelin sheath, CMT2 affects the axon. Because of this CMT2 is also known as 'axonal CMT'.

Symptoms are often first noticed between the ages of 10 and 20.

CMTX

CMTX is a variation of CMT1 and CMT2. It is called 'X' because the gene that causes this form of CMT is carried on the X chromosome. It usually affects men much more severely than women because a man has only one X chromosome and women have two. Men will usually develop symptoms beginning in late childhood or adolescence. Women may be completely unaffected, in which case they tend to be known as "carriers"; or they may be affected; but usually not as severely as males.

DI-CMT

DI stands for 'dominant intermediate' and this form of CMT is rare and usually has similar symptoms as the common versions of CMT1 and CMT2. The reason it is called intermediate is that both the myelin sheath and the axon are damaged equally.

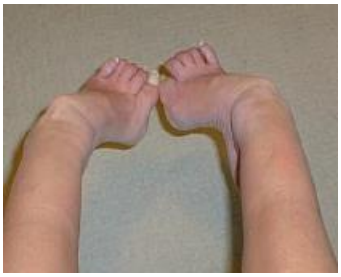
For both CMT1 and CMT2 there are many different subtypes and you may hear about CMT1A or CMT2AR, for example .These are all different genetic variations of the main types.

The symptoms of CMT

The exact symptoms that you may experience may vary hugely from other people with CMT – even within your own family. This is because there are many different genetic factors within individuals that influence the CMT genes. And it is perfectly possible that you may never have any symptoms, as anywhere between one in 10 and one in five people with CMT will never have any symptoms. (Some people may only get symptoms later in life, even if they have a type that 'normally' shows symptoms by the teenage years.)

All types tend to produce fairly similar symptoms.

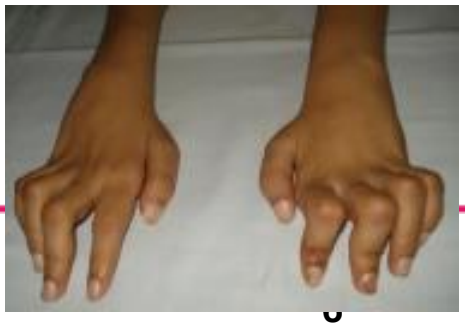
Early symptoms may include:



- slight difficulty walking because of problems picking up the feet (foot drop)
- children may experience difficulty with running and general agility before any other noticeable symptoms – including being "clumsy"
- high arches (some people will have abnormally flat feet), weak ankles and curled toes
- weakness in the hand and forearms, although the feet are usually affected first.

Other symptoms can include:

- some loss of feeling in the feet, lower legs, hands and forearms, although this is rarely troublesome
- loss of fine control in the hands, making it difficult to write, do fiddly things or open jars, for example
- some muscle tremor



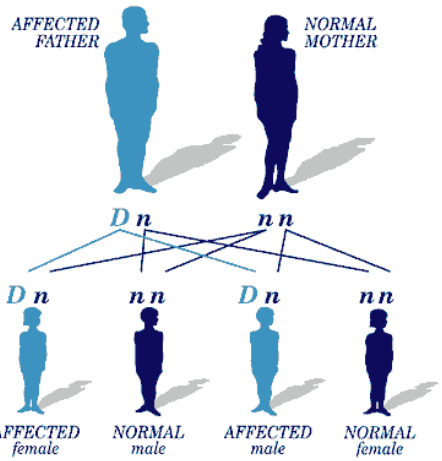
- tiredness (fatigue) because of the extra effort needed to do daily activities
- slight curve to the spine
- increased difficulty walking – aids may be needed, such as orthoses and walking sticks
- hip or knee problems.

Rarely, people with CMT can develop more severe symptoms .These can include:

- severe problems with mobility, necessitating the use of a wheelchair
- a severe curve of the spine (scoliosis)
- speech and swallowing difficulties
- some difficulty breathing, particularly at night.

Passing on our Genes and CMT

Inheritance patterns

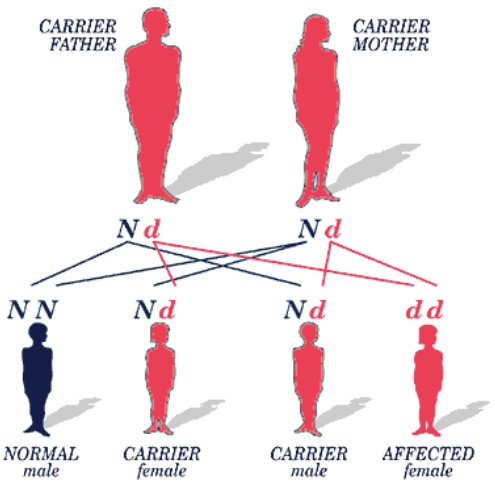


1 . **Dominant (autosomal dominant)**

Some faulty genes are dominant, which means that you only need one faulty gene to cause CMT .In effect the dominant gene overwrites the instructions from the 'good' gene.

The most common forms of CMT in the UK are dominant, including most forms of CMT1 and CMT2.

If you have a dominant form of CMT (regardless of your sex), you have a 50:50 chance of passing on the faulty gene to any children. If they inherit it, they will usually develop the symptoms of CMT at some point during their life. If they don't inherit it, they cannot pass CMT onto their children, as they don't carry the abnormal gene.



2 . Recessive (autosomal recessive)

If a faulty gene is recessive it means that you need two copies of the same faulty gene (one from each parent) before you could develop CMT.

If you only have one faulty recessive gene you are known as a carrier .You will not have CMT, but you have a 50:50 chance of passing on your faulty gene to your children. If they inherit it, they will only get CMT if they inherit a second faulty gene from the other parent.

Some forms of both CMT1 and CMT2 are recessive.

If your CMT is caused by two faulty recessive genes, you will definitely pass on one of your faulty genes to your children. But unless they inherit the same faulty gene from the other parent, they will only be a carrier.

If both parents are carriers for the same recessive gene, their children have a one in four chance of developing CMT (by inheriting two copies of the gene) and a 50 per cent chance of being carriers (by inheriting one copy of the gene).

3. X-linked

Of our 23 pairs of chromosomes, the 23rd pair is known as the sex chromosomes – either an X or a Y .If you inherit two X chromosomes you become a woman and if you inherit an X and a Y you become a man.

One faulty gene responsible for CMT has been discovered on the X chromosome. Men who get X-linked CMT are often more severely affected than women .A woman who is a carrier of X-linked CMT has a 50% chance of passing the gene onto her sons, and daughters will have a 50% chance of being a carrier (and could be mildly affected).

4. "De novo" mutation

Genes can change (mutate) 'out of the blue'. If this happens then with future generations will be exposed to the risk of inheriting the changed gene in just the same way as described above.

About one in 10 people with CMT1A have a new genetic mutation.

5. Sporadic CMT

The term sporadic is used when someone with CMT has apparently no family history (ie no other family members affected). This can be due to either a "de novo" mutation as explained above or because there are no other family members around to examine to see if they may be affected.

Summary of inheritance

You can inherit CMT in one of the following ways:

- if one parent has a dominant form of CMT
- if both parents are carriers of, or have, a recessive form of CMT
- if your mother has X-linked CMT
- if you are female and your father has X-linked CMT
- by a new mutation of the gene .("de novo" mutation)

Treating your CMT

At present, there is no specific treatment or cure for the underlying genetic cause of CMT. Neither are there any drugs to stop or reverse the damage caused to the peripheral nerves. But, although there is no cure for CMT, there are a number of treatments available. These can slow the development, or ease, some of the secondary complications linked to CMT, greatly improving your quality of life.

Good general advice is to look for the least invasive way to treat your problems using a combination of the following:

- Self-management
- Stretching and exercise.
- Healthy eating.
- Physical therapies
- Physiotherapy.
- Orthotics – the use of splints to support the joints
- Occupational therapy.
- Podiatry.
- Surgery

A consultant neurologist in partnership with your GP (general practitioner) should oversee your treatment.

The aim of all of these treatment options is two fold:

Prevent unnecessary problems

Through a combination of exercise, healthy eating, physiotherapy, occupational therapy and orthotics, the aim is to stop the primary symptoms of CMT developing into major secondary problems. Or limiting the way you live your life by causing problems such as having difficulty walking, back strain, difficulty handling things or uncomfortable ulcers on your feet.

Treat any problems quickly

If secondary problems do develop, such as severely arched feet or weak ankles, then orthotics, surgery, pain management, counselling and other adaptations or aids (eg, wheelchairs) may be helpful.

Because CMT is an ongoing condition, it is useful to be aware of the mechanics behind the condition to help prevent secondary complications developing. As always, prevention is better than treatment.

Further Reading

Charcot-Marie-Tooth: A Practical Guide

An essential guide to understand CMT, how to manage and treat the condition, and gives a wealth of practical information, including a directory of sources of further information.

This is a publication produced by CMT United Kingdom. ISBN 978-0-9533883-3-2

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