Muscular Dystrophy New Zealand

CHARCOT-MARIE-TOOTH DISEASE

What is Charcot-Marie-Tooth Disease?

First described in 1886 by three physicians – Jean-Marie Charcot, Pierre Marie, and Howard Henry Tooth, Charcot Marie-Tooth (CMT) is a group of relatively common genetic neurological conditions, occurring once in approximately 2,500 people. CMT is also known as Hereditary motor and sensory neuropathy (HMSN), or Peroneal Muscular Atrophy, and comprises a number of disorders that affect the peripheral nerves (eg. those of the hands and the lower legs). A nerve cell communicates information around the body by sending electrical signals down a long, thin part of the cell called the axon. In order to increase the speed at which these electrical signals travel, the axon is insulated by myelin, which is produced by another type of cell called the Schwann cell. Myelin twists around the axon and encourages the electrical signals. Without an intact axon and myelin sheath, peripheral nerve cells are unable to activate target muscles, or relay information from the limbs back to the brain.

CMT is caused by mutations in genes that produce proteins involved in the structure and function of either the peripheral nerve axon, or the myelin sheath. The degeneration of the peripheral nerves may result in a reduced ability to feel heat, cold, and pain. The gene mutations in CMT are usually inherited.

What are the different types of Charcot-Marie-Tooth Disease?

There are many forms of CMT disease. The principal types include CMT1, CMT2, CMT3, and CMT4.

CMT1 accounts for more than two-thirds of all cases of CMT, and with the exception of CMT1X, is inherited in an autosomal dominant pattern. CMT1 is caused by abnormal genes involved in the structure and function of myelin. This slows down the nerve conduction velocity. CMT1 has been further subdivided into CMT1A, CMT1B, CMT1C, CMT1D, CMT1F, and CMT1X. Hereditary neuropathy with liability to pressure palsies (HNPP) occurs on the same gene as CMT1A. CMT1 patients are slow runners in childhood, develop high arches, hammer toes and often require orthotics (braces) for ankle support. Varying degrees of hand weakness occur, often appearing as much as ten years after foot and leg problems. Problems with balance because of ankle weakness

and loss of proprioception are common. Most patients remain mobile throughout life and life expectancy is normal.

CMT2 is an autosomal dominant form of the condition in which nerve conduction velocities are usually in the normal range but occasionally fall below normal. CMT2 is caused by abnormal genes involved in the structure and function of axons. CMT2 has been further subdivided into CMT2A, CMT2B, CMT2C, CMT2D and CMT2E based on specific gene abnormalities. The clinical presentation is similar to CMT1: distal weakness, muscle atrophy, sensory loss and foot deformities. Patients with CMT2 have a wider age range for onset of the disorder and more variation in degree of disability. They are slightly more likely to maintain their deep tendon reflexes.

CMT3 is a particularly severe variant, also called Dejerine-Sottas. Individuals with this condition have been found to have a gene mutation in one of the genes responsible for CMT1A, CMT1B, CMT1D or CMT4. The term Dejerine-Sottas syndrome (DSS) is used to describe patients who have onset before three years of age, and have delayed motor milestones, as well as severe motor, sensory and skeletal defects. This form of CMT may be inherited in an autosomal recessive, or autosomal dominant pattern.

CMT4 is an autosomal recessive form of the condition. CMT4 has been further subdivided into CMT4A, CMT4B1, CMT4B2, CMT4C, CMT4D, CMT4E and CMT4F, based on specific gene abnormalities. All type 4 instances of CMT are considered rare. They can be either demyelinating or axonal, and have various phenotypical presentations. CMT4 disorders are more severe than autosomal dominantly inherited disorders. These disorders often have systemic conditions, such as cataracts and deafness.

What are the features of Charcot-Marie-Tooth Disease?

• A high arched foot is usually one of the first signs of this disorder, although in some instances extremely flat feet are also typical of CMT. As the disease progresses, structural foot deformities take place. The patient may develop a pes cavus (high-arched) foot and hammer toes (a condition in which the middle joint of a toe bends upwards).

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• The progressive muscle wasting in the lower legs lead to an "inverted champagne bottle" appearance, and problems with walking, running, and balance will be noticed. Ankle weakness and sprains are common, and many patients develop foot drop. To avoid tripping, patients with foot drop raise their knees unusually high, resulting in the high "steppage" gait associated with CMT. In some patients, muscle weakness may also occur in the upper legs.

• Later in the course of the disease, hand function may become affected. Progressive atrophy of the thenar muscle and the small muscles in the hand results in weakening or loss of the opposable pinch, and tasks requiring manual dexterity become difficult.

• Patients have problems holding pens and pencils, buttoning clothing, grasping zipper pulls and turning doorknobs. Many people benefit from occupational therapy which helps people accomplish the tasks of daily living with the use of assistive devices.

• The loss of nerve function is often accompanied by tingling and burning sensations in the hands and feet. This usually causes little more than mild discomfort, but some people experience severe neuropathic pain and require medication to control it.

• Loss of nerve function in the extremities can also result in sensory loss. The sense of touch is diminished, as is the ability to perceive changes in temperature, and patients may unknowingly injure themselves. They can be unaware of having developed ulcers of the feet or of cuts or burns on the hands. Sensory loss in CMT patients may also be • associated with dry skin and hair loss in the affected areas. In rare cases, sensory loss can lead to gradual hearing impairment and, sometimes, deafness.

• Many patients are extremely sensitive to the cold or even to temperatures a few degrees lower than normal. CMT results in the loss of insulating muscle mass, which, combined with reduced muscular activity and circulation, can leave patients with chronically cold hands and feet. Impairment of the normal circulatory process can also result in swelling (oedema) of the feet and ankles.

• Deep-tendon reflexes, such as the knee jerk reaction, are lost in many patients, and is of diagnostic importance. Some people with CMT also have tremor (usually of the

hands) and the combination of tremor and CMT is sometimes referred to as Roussy-Levy Syndrome.

• Weakness of the respiratory muscles is rare in people with CMT, but when present, it can cause lifethreatening problems. If shortness of breath is an issue, a patient should be checked by a respiratory specialist to see if the use of a ventilator is recommended.

• Another problem related to CMT can be scoliosis or mild curvature of the spine. This often occurs in puberty and tends to be most common in people with early onset of gait abnormalities. Hip dysplasia also affects a small number of CMT patients at an early age.

• The age of onset varies between types of CMT, with symptoms becoming apparent between the ages of five and fifteen for those with CMT1, and between ten and twenty for those with CMT2. CMT3 and 4 patients will usually experience onset before three years of age. The severity of symptoms can vary greatly from patient to patient, even within the same family. Some people may only discover they have CMT on diagnostic testing.

What causes Charcot-Marie-Tooth Disease?

The human genome consists of 23 paired chromosomes, which contain genes composed of DNA. 22 pairs of chromosomes are autosomes, meaning they are not involved in sex determination. The 23rd pair of chromosomes are the sex chromosomes, with males having one X and one Y chromosome, and females having two X chromosomes. There are three ways in which CMT can be inherited. Some forms of CMT are inherited in an autosomal dominant fashion, which means that only one copy of the abnormal gene is needed to cause the disease. Children of an affected parent have a 50% chance of inheriting the condition.

Other forms of CMT are autosomal recessive, which means that both copies of the abnormal gene must be present for the disease to develop fully. Thus, both parents must have the abnormal gene for their child to develop the disease. Each child they have has a 25% chance of inheriting the disease.

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Still other forms of CMT are inherited in an X-linked manner, which means that the abnormal gene is located on the X chromosome. Females, who have two X chromosomes, are able to compensate if one of their X chromosomes harbours the mutation. Males, who have one X and one Y chromosome lack this compensatory ability, and therefore
are more severely affected by the mutation. An affected male cannot pass on an Xlinked disorder to his sons, but his daughters will all be carriers.

In some cases, spontaneous mutations may occur randomly during a child's conception. Once they have occurred, the mutation can be passed onto subsequent generations by the affected parent.

For further information on genetics and how disorders are inherited, please refer to the Genetics Fact sheet available from the Muscular Dystrophy Association.

Diagnosis of Charcot-Marie-Tooth Disease

Diagnosis of CMT begins with a standard patient history, family history, and neurological examination. Patients will be asked about the nature and duration of their symptoms and whether other family members have the disease. During the neurological examination a physician will look for characteristic features of the disease and will then order diagnostic testing. These may include:

Electrodiagnostic Testing

Electrodiagnostic testing usually includes a nerve conduction velocity test (NCV), which measures the strength and speed of electrical signals moving down the peripheral nerves. Delayed responses are a sign of demyelination, and small responses are a sign of axonopathy. An electromyography (EMG) is another type of electrodiagnostic test, and is also used to measure the electrical signal's strength in the muscles of the arms or legs.

DNA Studies

These genetic tests, done by drawing blood, are available to test for many of the common chromosomal defects causing CMT. A positive genetic test can provide definitive diagnosis and provide useful information for family planning. However, a negative result does not rule out CMT since some forms are not yet able to be tested by

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DNA sampling. Currently, 18 types can be identified by DNA testing. Soon after the diagnosis of a CMT child, it is essential that genetic counselling is arranged, for one or both of two issues. The first is the probability that the mutation was inherited from the parents; and the second is whether testing for the condition in future pregnancies can be offered, and with what degree of reliability. Genetic counselling provides information about possible diagnostic tests, including prenatal testing. Genetic services are available in New Zealand and a referral can be made by the Muscular Dystrophy Association.

Management of Charcot-Marie-Tooth Disease

Although there is no cure for CMT at the present time, there are many therapies that can greatly improve life and function for CMT patients. After diagnosis, CMT patients are usually directed to: a podiatrist for the care of possible foot problems; an orthotist for the manufacture and fitting of braces; an orthopaedic surgeon for surgeries to straighten toes, lengthen heel cords or lower arches; or a physical therapist or occupational therapist to design exercise programs to strengthen muscles or learn energy conservation.

A good balanced diet is advised. No vitamins or dietary supplements are necessary unless a specific deficiency has been identified. Weight control is important, as any excessive weight will contribute to tiredness and weakness. The amount and type of food eaten by the individual should be monitored and adjusted to reflect energy needs. Maintaining a healthy weight will help the individual to move more easily and will assist caregivers who may have to lift them. It will also put less strain on the already weakened muscles.

People who have reduced to lost sensation in their hands and feet need to be very careful of the skin to prevent the occurrence of injuries. Hot cups should be handled with care, and the temperature of baths, hot water bottles and so on should be checked before being exposed to the skin.

There are some medications that should be avoided by people with CMT, as the can worsen the condition. The full list is available through MDA.

Research into Charcot-Marie-Tooth Disease

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Recent and ongoing research is aiming to identify new medications to treat the most common form of CMT - CMT1A and other demyelinating forms of CMT by looking for drugs that inhibit potassium channels in peripheral nerves. The Charcot-Marie-Tooth Association and the USA Muscular Dystrophy Association have joined forces to fund the first large-scale clinical trial in North America for the most common form of CMT, CMT1A.

Support for people with Charcot-Marie-Tooth Disease

Education

In New Zealand, every child has the right of equal access to all aspects of education. This means that all children with a neuromuscular condition have the right to attend a mainstream school. Many schools have special units attached which can provide any extra help needed, including an individualized education plan for appropriate assistance with physical and mental needs. It is important that CMT children are not overprotected or patronized – they should be mentally stimulated and creative skills encouraged.

Employment

Seeking and maintaining paid employment can be challenging for people with CMT, especially as their condition progresses. Despite these challenges many people in New Zealand with neuromuscular conditions carve out a career and work productively and successfully for a number of years. Research has shown that a paid occupation is achievable for others with the correct supports and environmental conditions (flexibility, adaptations, employer recognition, peer support).

When choosing a career, if possible choose something that you are passionate about and that meets your physical needs now and into the future as your condition progresses. Consider the workload; repetitive tasks, physicality of the job, or how much speaking is required if you struggle with slurred speech. Ask about opportunities for job shadowing to get a sense of daily tasks and expectations. Consider when are you more alert and more fatigued? Is there flexibility to work from home on certain days or to be flexible with work schedules so you can incorporate rests if needed? Will the job

accommodate flexibility to meet these needs so you can be more productive in your role?

Volunteer work is an opportunity to build up skills and experience. It creates the same feelings of self-worth, sense of identity and purpose as a paid job.

The New Zealand government recognises the value people with a disability can bring to a workforce and the under representation of this community in the labour market. They have set up a number of employment related services and supports for people with a disability, including training and apprenticeships. The list of all government-funded or supported services are available on the website Employment New Zealand.

Diversity Works New Zealand (formally the EEO Trust) is the national body for workplace diversity and inclusion. They can be contacted on 0800 348 377 or by visiting their website diversityworksnz.org.nz/

Remember, it is illegal for employers to discriminate against people because of ethnicity, sexual orientation, gender, marital status, religious belief, or disability. Equal rights are demanded by the Human Rights Act, 1993, and the Equal Pay Act, 1972. You can seek information about your rights on Health and Disability Commissioner website or Human Right Commission website.

For more information Muscular Dystrophy Association can be contacted for further information, assistance, advice, support and referrals, on 0800 800 337 or by e-mail at info@mda.org.nz

The Muscular Dystrophy Association Website also contains information on services available within NZ, our quarterly magazine, contacts, membership details, news and links to other sites - www.mda.org.nz

Further resources

www.hnf-cure.org – the Canadian Hereditary Neuropathy Foundation website contains excellent information.

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www.mdausa.org – the MDA USA website has an extensive site with plenty of further information on any muscular dystrophy conditions as well as research news.
www.cmt.org.uk – the UK CMT site. It contains good information on the condition. NZ also has an excellent website dedicated to helping and informing those families with rare disorders – www.nzord.org.nz

Information in this fact sheet was primarily sourced from: The Charcot-Marie-Tooth Association www.charcot-marie-tooth.org
The National Institute of Neurological Disorders and Stroke
http://www.ninds.nih.gov/disorders/charcot_marie_tooth/

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