Charcot-Marie-Tooth Disease

U.S. DEPARTMENT OF HEALTH
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What is Charcot-Marie-Tooth disease?

Charcot-Marie-Tooth disease (CMT) is one of a group of disorders that cause damage to the peripheral nerves—the nerves that transmit information and signals from the brain and spinal cord to and from the rest of the body, as well as sensory information such as touch back to the spinal cord and brain. CMT can also directly affect the nerves that control the muscles. Progressive muscle weakness typically becomes noticeable in adolescence or early adulthood, but the onset of disease can occur at any age. Because longer nerves are affected first, symptoms usually begin in the feet and lower legs and then can affect the fingers, hands, and arms. Most individuals with CMT have some amount of physical disability, although some people may never know they have the disease.

CMT, also known as hereditary motor and sensory neuropathy, is one of the most common inherited neurological disorders, affecting an estimated 126,000 individuals in the United States and 2.6 million people worldwide. Nearly all cases are inherited. It is possible to have two or more types of CMT, which happens when the person has mutations in

two or more genes, each of which causes a form of the disease. CMT is a heterogenous genetic disease, meaning mutations in different genes can produce similar clinical symptoms. CMT is named for the three physicians who described it in 1886.

There is currently no cure for CMT but it can be managed with supportive therapy. CMT isn't usually life-threatening and rarely affects muscles involved in vital functions like breathing. People with most forms of CMT have a normal life expectancy.

What causes Charcot-Marie-Tooth disease?

A nerve cell communicates information to distant targets by sending electrical signals down a long, thin part of the cell called the axon. The axon is surrounded by myelin, a covering that acts like the insulation on an electrical wire and aids the high-speed transmission of electrical signals. Without an intact axon and myelin sheath, signals that run along the nerve and axon are either slow or have a weak signal, meaning that the peripheral nerve cells become unable to activate muscles or relay sensory information from the limbs back to the spinal cord and the brain.

CMT is caused by mutations in genes that support or produce proteins involved in the structure and function of either the peripheral nerve axon or the myelin sheath. More than 40 genes have been identified in CMT, with each gene linked to one or more types of the

disease. In addition, multiple genes can be linked to one type of CMT. More than half of all cases of CMT are caused by a duplication of the PMP22 gene on chromosome 17.

Although different proteins are abnormal in different forms of CMT disease, all of the mutations mainly affect the normal function of the peripheral nerves. Gene defects in myelin cause dysfunction of the coating, which distorts or blocks nerve signals, while other mutations limit axon function and cause axonal loss.

What are the symptoms of Charcot-Marie-Tooth disease?

CMT affects both sensory and motor nerves (nerves that trigger an impulse for a muscle to contract) in the arms, hands, legs, and feet. The affected nerves slowly degenerate and lose the ability to communicate with their distant targets. Motor nerve degeneration results in muscle weakness and decrease in muscle bulk (atrophy) in the arms, legs, hands, or feet.

Typical early features include weakness or paralysis of the foot and lower leg muscles, which can cause difficulty lifting the foot (foot drop) and a high-stepped gait with frequent tripping or falling. Individuals also may notice balance problems. Foot deformities, such as high arches and curled toes (hammertoes), are also common in CMT. The lower legs may take on an "inverted champagne bottle" shape due to the loss of muscle bulk. As the disease

progresses, weakness and atrophy may occur in the hands, causing difficulty with fine motor skills. Degeneration of sensory nerve axons may result in a reduced ability to feel heat, cold, and touch. The senses of vibration and position (proprioception) are often decreased in individuals with CMT. The disease also can cause curvature of the spine (scoliosis) and hip displacement. Many people with CMT develop contractures—chronic shortening of muscles or tendons around joints, which prevents the joints from moving freely. Muscle cramping is common. Nerve pain can range from mild to severe, and some individuals may need to rely on foot or leg braces or other orthopedic devices to maintain mobility. Some people with CMT experience tremor, and vision and hearing can also be affected. In rare cases, breathing difficulties may occur if the nerves that control the muscles of the diaphragm are affected.

The severity of symptoms can vary greatly among individuals and even among family members with the disease and gene mutation. Progression of symptoms is gradual.

How is CMT inherited?

The gene mutations in CMT are inherited in three distinct patterns: autosomal dominant, autosomal recessive, and X-linked, all of which are tied to a person's chromosomes. Each person has 23 pairs of chromosomes. The first 22 pairs are called "autosomes" and

are inherited independently of the person's biological sex. Each individual normally possesses two copies of every gene on the autosomes, one inherited from each parent. Autosomal dominant means only one copy of the CMT gene—from either parent—is needed to get the disease, and a child of an affected parent (either mother or father) has a 50 percent chance of inheriting the disorder. Autosomal recessive disorders happen when a child receives two mutated genes, one from each parent; neither parent would normally have the disease. Their children have a 25 percent chance of inheriting the disease. Autosomal disorders, both dominant and recessive, affect males and females equally.

Other types of CMT are inherited in an X-linked fashion, meaning they are dependent on the chromosomes that determine a person's sex. Women have two X chromosomes, one inherited from each parent. Men have an X and a Y chromosome, with the Y chromosome being inherited from the father. A son of a mother who carries a disorder on one of her X chromosomes has a 1 in 2 chance of inheriting the disorder.

In some cases a new mutation occurs spontaneously in the person's genetic material during conception, without having been passed down through the family. The new mutation can then be passed to an individual's children.

What are the types of Charcot-Marie-Tooth disease?

There are many different types of CMT disease, which may share some symptoms but vary by pattern of inheritance, age of onset, and whether the axon or myelin sheath is involved.

CMT1 is caused by abnormalities in the myelin sheath. The autosomal dominant disorder has six main subtypes.

- CMT1A results from a duplication of the gene on chromosome 17 that carries the instructions for producing the peripheral myelin protein-22 (PMP22). The PMP22 protein is a critical component of the myelin sheath. Overexpression of this gene causes the abnormal structure and function of the myelin sheath. CMT1A is usually slowly progressive. Individuals experience weakness and atrophy of the muscles of the lower legs beginning in childhood; later they experience hand weakness, sensory loss, and foot and leg problems. A different neuropathy distinct from CMT1A called *hereditary neuropathy with predisposition to pressure palsy* (HNPP) is caused by a deletion of one of the PMP22 genes. In this case, abnormally low levels of the PMP22 gene result in episodic, recurrent demyelinating neuropathy.

- CMT1B is caused by mutations in the gene that carries the instructions for manufacturing the myelin protein zero (MPZ, also called P0), which is another critical component of the myelin sheath. Most of these mutations are point mutations, meaning a mistake occurs in only one letter of the DNA genetic code. To date, scientists have identified more than 120 different point mutations in the P0 gene. CMT1B produces symptoms similar to those found in CMT1A.
- Other less common causes of CMT1 result from mutations within the SIMPLE (also called LITAF), EGR2, PMP22, and NEFL genes, respectively.

CMT2 results from abnormalities in the axon of the peripheral nerve cell, rather than the myelin sheath, and is less common than CMT1. This autosomal dominant disorder has more than a dozen subtypes (some of which have their own variants), with each subtype being associated with mutations in a specific gene. Symptoms are similar to those seen in CMT1, but people with CMT2 often have less disability and sensory loss than individuals with CMT1. The onset of CMT2 is usually in childhood or adolescence. Some types of CMT2 may have vocal cord or phrenic nerve involvement, causing speech or breathing problems.

CMT3, or **Dejerine-Sottas disease**, is a particularly severe demyelinating neuropathy that begins in infancy. Infants have severe muscle atrophy, weakness, delayed motor skills development, and sensory problems. Symptoms may progress to severe disability, loss of sensation, and curvature of the spine. This rare disorder can be caused by mutations in multiple genes, including PMP22, MPZ, and EGR2, and can be inherited either dominantly or recessively.

CMT4 comprises several different subtypes of demyelinating and axonal and motor neuropathies that are inherited autosomal recessively. Each neuropathy subtype is caused by a mutation in a different gene (several genes have been identified in CMT4). The mutations may affect a particular ethnic population and produce distinct physiologic or clinical characteristics. People with CMT4 generally develop symptoms of leg weakness in childhood and by adolescence they may not be able to walk. CMT4 is rare in the United States.

CMTX1 (also called CMT X, Type 1) is the second most common form of CMT. This X-linked disease is caused by mutations in a gene that provides instructions for making the protein connexin-32. The connexin-32 protein is found in myelinating Schwann cells—cells that wrap around nerve axons and make up the myelin sheath. Males who inherit the mutated gene show moderate to severe symptoms of the disease

beginning in late childhood or adolescence. Females who inherit a mutated gene often develop milder symptoms than males or do not show symptoms.

How is Charcot-Marie-Tooth disease diagnosed?

Diagnosis of CMT begins with a detailed medical history, family history, and neurological examination. A physician will look for evidence of muscle weakness in the arms, legs, hands, and feet, decreased muscle bulk, reduced tendon reflexes, and sensory loss. The physician will also look for evidence of foot deformities and other orthopedic problems, such as mild scoliosis or an abnormal formation of the hip joint. A specific sign that may be found in individuals with CMT1 is nerve enlargement that may be felt or even seen through the skin, especially at the elbow. These enlarged nerves, called hypertrophic nerves, are caused by abnormally thickened myelin sheaths.

The physician may order nerve conduction studies and electromyography (EMG). During nerve conduction studies, electrodes are placed on the skin over a muscle or nerve. These electrodes produce a small electric impulse that stimulates nerves and provides quantifiable information by capturing electrical activity from a distal muscle or nerve (those in the hands, lower arms, lower legs, and feet) that can help the doctor to arrive at a diagnosis. EMG involves inserting a needle electrode

through the skin to the muscle and measuring the bioelectrical activity of muscles. Specific abnormalities in the readings signify axon loss. EMG may be useful in further characterizing the distribution, activity, and severity of peripheral nerve involvement.

Genetic testing, which involves analyzing a blood sample, can detect the most common types of CMT (DNA tests are not currently available for all types of CMT).

A nerve biopsy involves removing and analyzing a small piece of peripheral nerve under the microscope, usually taken from the calf of the leg through an incision in the skin. People with CMT1 typically show signs of abnormal myelination. Specifically, formations that look like onion bulbs may be seen which represent axons surrounded by layers of remyelinating Schwann cells. People with CMT2 usually show signs of axon degeneration without evidence of demyelination.

How is Charcot-Marie-Tooth disease treated?

There is no cure for CMT, but physical and occupational therapies, braces and other orthopedic devices, and orthopedic surgery can help people cope with the disabling symptoms of the disease. In addition, pain-relief drugs can be prescribed for individuals who have severe nerve pain.

Maintaining mobility, flexibility, and muscle strength is important. Beginning a treatment program early may delay or reduce nerve degeneration and muscle weakness before it progresses to the point of disability. Physical therapy includes muscle strength training, muscle and ligament stretching, and moderate aerobic exercise. A specialized exercise program approved by the person's physician can help build stamina, increase endurance, and maintain overall health.

Many individuals with CMT require ankle braces and other orthopedic devices to maintain everyday mobility and prevent injury. Braces can help prevent ankle sprains by providing support and stability during activities such as walking or climbing stairs. High-top shoes or boots also can give the person support for weak ankles. Thumb splints can help with hand weakness and loss of fine motor skills. Assistive devices should be used before disability sets in because the devices may prevent muscle strain and reduce muscle weakening.

Some people with CMT may decide to have orthopedic surgery to treat severe foot and joint deformities, improve the ability to walk, and lessen pain.

Occupational therapy involves learning new ways to cope with the activities of daily living. For example, individuals with weakness in their arms and hands may learn to use Velcro closures or clasps instead of buttons on their clothes, or new ways of feeding themselves using assistive technology.

What research is being done?

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. The NINDS is a component of the National Institutes of Health (NIH), the leading supporter of biomedical research in the world.

Ongoing research on CMT includes efforts to identify more of the mutant genes and proteins that cause the various disease subtypes, discover the mechanisms of nerve degeneration and muscle atrophy with the goal of developing interventions to stop or slow down these debilitating processes, and develop therapies to reverse nerve degeneration and muscle atrophy.

The NINDS supports the NIH's Rare Diseases Clinical Research Network, which is made up of different research consortia aimed at improving the availability of rare diseases information, clinical studies, and clinical research information. The Network's Inherited Neuropathies Consortium conducts studies that include a natural history analysis of CMT, the search for new genes and those that modify an individual's symptoms, therapy development, and training programs to educate future investigators for the inherited neuropathies. For more information on the Rare Diseases Clinical Research Network and its consortia, see http://rarediseases.info.nih.gov.

Scientists are studying PMP22 gene regulation to design and validate assays that measure the presence, amount, or activity of a target object. Other studies examine the effects of small molecules on the biological system in order to develop novel treatments. High-throughput screens (a way to quickly assess the biological activity of large numbers of compounds) may identify candidate medications that reduce PMP22 levels. Additional research focuses on how the mitochondria, the cell's power plant, may play a role in the axonal degeneration seen in CMT, as well as other diseases.

An NIH longitudinal collaborative study hopes to determine the natural history of CMT and how the presence of a certain gene mutation may result in disease types and symptoms. Also, a two-part study is looking for new genes that cause the disease as well as genes that do not cause the disease but may modify a person's symptoms. Other NIH-funded scientists are using next-generation sequencing (which can quickly identify the structure of millions of small fragments of DNA at the same time) to identify novel CMT genes.

Gene therapy is another promising area of research. Experiments involving cell cultures and animal models of the disease have shown that it is possible to deliver genes to Schwann cells and muscles. Other studies show trophic factors or nerve growth factors, such as the hormone androgen that prevent nerve degeneration.

Where can I get more information?

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN
P.O. Box 5801
Bethesda, MD 20824
301-496-5751
800-352-9424
www.ninds.nih.gov

Information also is available from the following organizations:

Charcot-Marie-Tooth Association
P.O. Box 105
Glenolden, PA 19036
610-499-9264
800-606-2682
www.charcot-marie-tooth.org

Hereditary Neuropathy Foundation
432 Park Avenue South, 4th Floor
New York, NY 10016
212-722-8396
855-435-7268
www.hnf-cure.org

Muscular Dystrophy Association
3300 East Sunrise Drive
Tucson, AZ 85718-3208
520-529-2000
800-572-1717
www.mda.org

Genetics Home Reference
National Library of Medicine, NIH
http://ghr.nlm.nih.gov

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