Charcot-Marie-Tooth Disease

What is Charcot-Marie-Tooth disease? Charcot-Marie-Tooth disease (CMT) is one of the most common inherited neurological disorders, affecting approximately 1 in 2,500 people in the United States. The disease is named for the three physicians who first identified it in 1886 - Jean-Marie-Charcot and Pierre Marie in Paris, France, and Howard Henry Tooth in Cambridge, England. CMT, also known as hereditary motor and sensory neuropathy (HMSN) or peroneal muscular atrophy, comprises a group of disorders that affect peripheral nerves. The peripheral nerves lie outside the brain and spinal cord and supply the muscles and sensory organs in the limbs. Disorders that affect the peripheral nerves are called peripheral neuropathies.

What are the symptoms of Charcot-Marie-Tooth disease? The neuropathy of CMT affects both motor and sensory nerves. A typical feature includes weakness of the foot and lower leg muscles, which may result in foot drop and a high-stepped gait with frequent tripping or falls. Foot deformities, such as high arches and hammertoes (a condition in which the middle joint of a toe bends upwards) are also characteristic due to weakness of the small muscles in the feet. In addition, the lower legs may take on an “inverted champagne bottle” appearance due to the loss of muscle bulk. Later in the disease, weakness and muscle atrophy may occur in the hands, resulting in difficulty with fine motor skills.

Onset of symptoms is most often in adolescence or early adulthood, however presentation may be delayed until mid-adulthood. The severity of symptoms is quite variable in different patients and some people may never realize they have the disorder. Progression of symptoms is very gradual. CMT is not fatal and people with most forms of CMT have a normal life expectancy.

What are the types of Charcot-Marie-Tooth disease? There are many forms of CMT disease. The principal types include CMT1, CMT2, CMT3, CMT4, and CMTX. CMT1 is the most frequent and results from abnormalities in the myelin sheath. There are three main types of CMT1. CMT1A is an autosomal dominant disease resulting from a duplication of the gene on chromosome 17 that carries the instructions for producing the peripheral myelin protein-22 (PMP-22). The PMP-22 protein is a critical component of the myelin sheath. An overabundance of this gene causes the structure and function of the myelin sheath to be abnormal. Patients experience weakness and atrophy of the muscles of the lower legs beginning in adolescence; later they experience hand weakness and
sensory loss. Interestingly, a different neuropathy distinct from CMT1A called hereditary neuropathy with predisposition to pressure palsy (HNPP) is caused by a deletion of one of the PMP-22 genes. In this case abnormally low levels of the PMP-22 gene result in episodic, recurrent demyelinating neuropathy. CMT1B is an autosomal dominant disease caused by mutations in the gene that carries the instructions for manufacturing the myelin protein zero (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 30 different point mutations in the P0 gene. As a result of abnormalities in P0, CMT1B produces symptoms similar to those found in CMT1A. The gene defect that causes CMT1C, which also has symptoms similar to those found in CMT1A, has not yet been identified.

CMT2 results from abnormalities in the axon of the peripheral nerve cell rather than the myelin sheath. There are many subtypes of CMT2, designated by the letters from A-L. Each subtype is characterized by the mode of inheritance and associated clinical features. The genetic loci have been identified for some subtypes. Recently, a mutation was identified in the gene that codes for the kinesin family member 1B-beta protein in families with CMT2A. Kinesins are proteins that act as motors to help power the transport of materials along the train tracks (microtubules) of the cell. Another recent finding is a mutation in the neurofilament-light gene, identified in a Russian family with CMT2E. Neurofilaments are structural proteins that help maintain the normal shape of a cell.

CMT3 or Dejerine-Sottas disease is a severe demyelinating neuropathy that begins in infancy. Infants have severe muscle atrophy, weakness, and sensory problems. This rare disorder can be caused by a specific point mutation in the P0 gene or a point mutation in the PMP-22 gene.

CMT4 comprises several different subtypes of autosomal recessive demyelinating motor and sensory neuropathies. Each neuropathy subtype is caused by a different genetic mutation, may affect a particular ethnic population, and produces distinct physiologic or clinical characteristics. Patients with CMT4 generally develop symptoms of leg weakness in childhood and by adolescence they may not be able to walk. The gene abnormalities responsible for CMT4 have yet to be identified.

CMTX is an X-linked dominant disease and is caused by a point mutation in the connexin-32 gene on the X chromosome. The connexin-32 protein is
expressed in Schwann cells—cells that wrap around nerve axons, making up a single segment of the myelin sheath. This protein may be involved in Schwann cell communication with the axon. Males who inherit one mutated gene from their mothers show moderate to severe symptoms of the disease beginning in late childhood or adolescence (the Y chromosome that males inherit from their fathers does not have the connexin-32 gene). Females who inherit one mutated gene from one parent and one normal gene from the other parent may develop mild symptoms in adolescence or later or may not develop symptoms of the disease at all.

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. 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 like a jelly-roll cake and prevents dissipation of the electrical signals. Without an intact axon and myelin sheath, peripheral nerve cells are unable to activate target muscles or relay sensory 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. Although different proteins are abnormal in different forms of CMT disease, all of the mutations affect the normal function of the peripheral nerves. Consequently, these nerves slowly degenerate and lose the ability to communicate with their distant targets. The degeneration of motor nerves results in muscle weakness and atrophy in the extremities (arms, legs, hands, or feet), and the degeneration of sensory nerves results in a reduced ability to feel heat, cold, and pain.

The gene mutations in CMT disease are usually inherited. Each of us normally possesses two copies of every gene, one inherited from each parent. 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. Other forms of CMT are inherited in an autosomal recessive fashion, which means that both copies of the abnormal gene must be present to cause the disease. Still other forms of CMT are inherited in an X-linked fashion, which means that the abnormal gene is located on the X chromosome. The X and Y chromosomes determine an individual’s sex. Individuals with two X chromosomes are female and individuals with one X and one Y chromosome are male. In rare cases the gene mutation causing CMT disease is a new mutation which occurs
spontaneously in the patient’s genetic material and has not been passed down through the family.

How is Charcot-Marie-Tooth disease diagnosed? 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 evidence of muscle weakness in the arms, legs, hands, and feet, decreased muscle bulk, reduced tendon reflexes, and sensory loss. Doctors look for evidence of foot deformities, such as high arches, hammertoes, inverted heel, or flat feet. Other orthopedic problems, such as mild scoliosis or hip dysplasia, may also be present. A specific sign that may be found in patients with CMT1 is nerve enlargement that may be felt or even seen through the skin. These enlarged nerves, called hypertrophic nerves, are caused by abnormally thickened myelin sheaths.

If CMT is suspected, the physician may order electrodiagnostic tests for the patient. This testing consists of two parts: nerve conduction studies and electromyography (EMG). During nerve conduction studies, electrodes are placed on the skin over a peripheral motor or sensory nerve. These electrodes produce a small electric shock that may cause mild discomfort. This electrical impulse stimulates sensory and motor nerves and provides quantifiable information that the doctor can use to arrive at a diagnosis. EMG involves inserting a needle electrode through the skin to measure the bioelectrical activity of muscles. Specific abnormalities in the readings signify axon degeneration. EMG may be useful in further characterizing the distribution and severity of peripheral nerve involvement.

If all other tests seem to suggest that a patient has CMT, a neurologist may perform a nerve biopsy to confirm the diagnosis. A nerve biopsy involves removing a small piece of peripheral nerve through an incision in the skin. This is most often done by removing a piece of the nerve that runs down the calf of the leg. The nerve is then examined under a microscope. Patients with CMT1 typically show signs of abnormal myelination. Specifically, “onion bulb” formations may be seen which represent axons surrounded by layers of demyelinating and remyelinating Schwann cells. Patients with CMT2 usually show signs of axon degeneration.

Genetic testing is available for some types of CMT and may soon be available for other types; such testing can be used to confirm a diagnosis. In addition, genetic counseling is available to parents who fear that they
may pass mutant genes to their children.

How is Charcot-Marie-Tooth disease treated? There is no cure for CMT, but physical therapy, occupational therapy, braces and other orthopedic devices, and even orthopedic surgery can help patients cope with the disabling symptoms of the disease. In addition, pain-killing drugs can be prescribed for patients who have severe pain.

Physical and occupational therapy, the preferred treatment for CMT, involves muscle strength training, muscle and ligament stretching, stamina training, and moderate aerobic exercise. Most therapists recommend a specialized treatment program designed with the approval of the patient’s physician to fit individual abilities and needs. Therapists also suggest entering into a treatment program early; muscle strengthening may delay or reduce muscle atrophy, so strength training is most useful if it begins before nerve degeneration and muscle weakness progress to the point of disability.

Stretching may prevent or reduce joint deformities that result from uneven muscle pull on bones. Exercises to help build stamina or increase endurance will help prevent the fatigue that results from performing everyday activities that require strength and mobility. Moderate aerobic activity can help to maintain cardiovascular fitness and overall health. Most therapists recommend low-impact or no-impact exercises, such as biking or swimming, rather than activities such as walking or jogging, which may put stress on fragile muscles and joints.

Many CMT patients require ankle braces and other orthopedic devices to maintain everyday mobility and prevent injury. Ankle braces can help prevent ankle sprains by providing support and stability during activities such as walking or climbing stairs. High-top shoes or boots can also give the patient 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 CMT patients may decide to have orthopedic surgery to reverse foot and joint deformities.

What research is being done? The NINDS supports research on CMT and other peripheral neuropathies in an effort to learn how to better treat, prevent, and even cure these disorders. Ongoing research includes efforts to identify more of the mutant genes and proteins that cause the various disease subtypes, efforts to discover the mechanisms of nerve degeneration and muscle atrophy with the hope of developing interventions to stop or slow down these debilitating processes, and efforts
to find therapies to reverse nerve degeneration and muscle atrophy.

One promising area of research involves gene therapy experiments. Research with cell cultures and animal models has shown that it is possible to deliver genes to Schwann cells and muscle. Another area of research involves the use of trophic factors or nerve growth factors, such as the hormone androgen, to prevent nerve degeneration.

Where can I get more information? Charcot-Marie-Tooth Association (CMTA) 610-499-9264 800-606-CMTA (2682) www.charcot-marie-tooth.org

Muscular Dystrophy Association 520-529-2000 800-572-1717 www.mdausa.org

Neuropathy Association 60 East 42nd Street, Suite 942 New York, NY 10165-0999 212-692-0662 800-247-6968 www.neuropathy.org

National Ataxia Foundation (NAF) 2600 Fernbrook Lane North, Suite 119 Minneapolis, MN 55447-4752 763-553-0020 http://www.ataxia.org/

This information was developed by the Office of National Institute of Neurological Disorders and Stroke, National Institute of Health.