Charcot-Marie-Tooth disease type X

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Introduction

This article includes discussion of Charcot-Marie-Tooth disease type X, CMT1X, hereditary motor and sensory neuropathy X, hereditary motor and sensory neuropathy type X, X-linked Charcot-Marie-Tooth disease, and X-linked CMT. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

X-linked Charcot-Marie-Tooth disease (CMT1X) is the second most common form of inherited neuropathy. Patients develop a progressive distal weakness and atrophy that results from length-dependent axonal loss. More than 400 different mutations in *GJB1*, the gene that encodes the gap junction protein connexin32, cause CMT1X. Most mutations result in defective function of the gap junctions formed by Cx32. In addition to the demyelinating neuropathy, many patients have subclinical CNS findings, and a few *GJB1* mutations are associated with striking, transient CNS manifestations.

Key points

- Charcot-Marie-Tooth disease type X is the second most common form of Charcot-Mari--Tooth disease.
- Men are more affected than women; women are variably affected.
- Intermediate conduction slowing (25 to 40 m/sec) is characteristic for men; slowing is typically less pronounced in women.
- Charcot-Marie-Tooth disease type X is caused by mutations in GJB1, the gene that encodes connexin32.

Historical note and terminology

Shortly after the first descriptions of autosomal dominant kindreds with inherited neuropathy by Charcot, Marie, and Tooth in 1886, Herringham described a family in which males were selectively affected (Herringham 1888). He noted the similarity of the affected men to the individuals described by Charcot, Marie, and Tooth, and was struck by the finding that the women who passed the trait of their fathers to their own sons were themselves unaffected. "This form makes one wonder what inheritance is. That the diseased tissues of a consumptive father should be so represented in his spermatozoon as to cause his child to fall into consumption is remarkable enough. But that the women of this family, themselves even uncommonly buxom and healthy, should be able to select their children, and transmit to the males alone tissues unlike their own, and endowed with a regular form of weakness that they do not themselves possess, is still more marvelous. It seems as if the daughter of a diseased father carried from the beginning of her life ova of 2 sexes, the female healthy, the male containing within it the representation of the father's disease." What makes Herringham's analysis so prescient is that in 1889, Mendel's discovery of autosomal inheritance was unheralded and Morgan's demonstration of X-linked inheritance did not appear until 1910.

Dominantly inherited, non-syndromic neuropathies are called Charcot-Marie-Tooth disease (CMT) or hereditary motor and sensory neuropathy (Shy et al 2005; Fridman and Reilly 2015). Most forms of Charcot-Marie-Tooth disease have slowly progressive, length-dependent weakness, atrophy, and sensory loss, including reduction of deep tendon reflexes. On the basis of the clinical features, nerve conduction velocities, and histopathology, Charcot-Marie-Tooth disease was subdivided into 2 types: type 1 (demyelinating) and type 2 (axonal). Subsequent linkage studies led to the further subdivision of CMT1 into distinct genetic forms: CMT1A (linked to chromosome 17), CMT1B (linked to chromosome 1), CMT1C (linked to chromosome 16), and CMT1X (linked to the X chromosome). Mutations in *PMP22*, *MPZ*, *LITAF*/*SIMPLE*, *EGR2*, *GJB1*, and *PMP2* cause CMT1; this list is likely incomplete because a few CMT1 patients do not have mutations in these genes (Fridman et al 2015). All of these genes are expressed by myelinating Schwann cells and are thought to cause disease through their effects in myelinating Schwann cells (Scherer and Wrabetz 2008). Although demyelination is the initial effect of these mutations, the severity of all of these neuropathies is directly related to the degree of axonal loss rather than demyelination per se (Lewis et al 2003).

Clinical manifestations

Presentation and course

In males, symptoms typically begin in childhood or adolescence. The initial symptoms include difficulty running and frequently sprained ankles; foot drop and sensory loss in the legs develop later. Depending on the tempo of the disease, the distal weakness may progress to involve the gastrocnemius and soleus muscles, even to the point where assistive devices are required for ambulation.{embed="pagecomponents/media_embed" entry_id="9676"} Weakness, atrophy, and sensory loss also develop in the hands, particularly in thenar muscles. These clinical manifestations are the result of a chronic, length-dependent axonal loss and are nearly indistinguishable from those seen in patients with CMT1A or CMT1B, although atrophy, particularly of intrinsic hand muscles, positive sensory phenomena, and sensory loss may be more prominent in CMT1X patients (Scherer and Kleopa 2005). Neurologic examination also reveals diminished to absent reflexes and sensory impairment, all of which are length-dependent and worsen insidiously over time but to varying degrees in different patients. Pes cavus, varus deformities, and "hammer toes" are frequently present.

Female carriers may be asymptomatic; if affected, they usually have a later onset and are less affected than males of the same age (Siskind et al 2011). The reason that female carriers are less affected probably owes to X-inactivation; only a fraction of their myelinating Schwann cells express the mutant *GJB1* allele (Scherer et al 1998). A few kindreds have been reported to have recessive CMT1X, but even in these kindreds, most obligate carriers have electrophysiological evidence of peripheral neuropathy (Hahn et al 1990).

These clinical manifestations, including their age-related progression, are described in the clinical vignette.

Prognosis and complications

CMT1X typically does not affect longevity. Regardless of the mutation, affected men have a similar degree of impairment, but one cannot predict the degree to which a presymptomatic woman will be affected (Siskind et al 2011).

There are a few potential complications. Ionasescu and colleagues reported "breathing difficulty due to phrenic nerve involvement" in severe cases of CMT1X, but no details were provided (Ionasescu et al 1996; Ionasescu 1998). Scoliosis has been reported in patients with Charcot-Marie-Tooth disease, including CMT1X (Horacek et al 2007). Although skin breakdown and trophic ulcers do not appear to be as problematic as in other neuropathies, it is prudent to advise patients about foot care. Pain and autonomic involvement are not prominent features of CMT1X. Patients with CMT1X have not been reported to develop a superimposed inflammatory demyelinating neuropathy.

Patients with any inherited neuropathy may be at increased risk of developing neuropathy if they are exposed to agents that can cause neuropathy. This potential hazard is exemplified by patients with CMT1A who develop severe vincristine neuropathy. Thus, drugs that can cause neuropathy should be avoided if possible; these include vincristine, cisplatin, taxol, suramin, colchicine, metronidizole, amiodarone, disulfiram, nitrofurantoin, isoniazid, dapsone, perhexiline, thalidomide, and "mega-doses" of pyridoxine (vitamin B6). Cisplatin (Cowie and Barrett 2001) and even vincristine (Ajitsaria et al 2007), however, have been given to CMT1X patients without obvious complications, but there is a brief report that the combination of vincristine and voriconazole worsened the neuropathy in a 5-year-old girl with CMT1X (Porter et al 2008).

Clinical vignette

The following 4 paragraphs are excerpted from a description of a CMT1X family by Hahn and colleagues (Hahn et al 1990); this family has a Tyr211stop mutation in *GJB1*.

Patient A. On examination, this 61-year-old male reported that the onset of his symptoms dated back to early childhood, when he noted awkwardness and difficulty in running. He always had highly arched feet. In his teens, the muscles in his lower legs became thin, and he frequently twisted his ankles. His penmanship was always poor, and his fingers and hands were clumsy, particularly in cold weather. Over the years, his symptoms progressed insidiously, and he developed pain and sensations of pins and needles in his feet and intermittently in his fingers. The hand muscles became progressively wasted, and his fingers became so clawed that he had poor use of his hands and could not even sign his name. A triple arthrodesis, performed in both feet at age 38 years, improved his walking, yet in the past 10

years, walking had become more difficult and he had to use 2 sticks. On examination there was marked wasting and weakness of the hand muscles, in particular the thenar muscles, and of all muscles below the knee. There was pes cavus and varus deformity. Tendon reflexes were depressed in the arms and at the knees, and ankle jerks were absent. There was a graded sensory loss to just above the wrist and to the knee. His gait was unsteady with bilateral foot drop.

Patient B. On examination, this 14-year-old male reported that he had difficulty running even when in kindergarten, when his feet were already highly arched. Between the ages of 8 and 10 years, his gait became increasingly awkward. He tripped easily and tended to walk on the lateral edge of the foot. He had difficulty using his hands in cold weather and needed help with shoelaces and buttons. On examination, there was mild wasting and weakness of the hand muscles, in particular the thenar muscles. His feet were highly arched with marked hammer toe formation and extensive callosities on the lateral foot borders. Peroneal and anterior tibial muscles, and to a lesser extent the gastrocnemius muscles, were wasted, and he was unable to dorsiflex his ankle. His tendon reflexes were depressed, and the ankle jerks were absent. All modalities of sensation were reduced to wrist and midcalf levels. Cutaneous nerves were not enlarged.

Patient C. On examination, this 37-year-old mother of Patient B reported that she was clumsy when running as a child and was never able to ice skate. In her late teens, her fingers felt awkward in cold weather and she had trouble buttoning her clothes. Her feet were always highly arched, but recently she had developed increasing hammer toes, and she had a tendency to sprain her ankles. Her feet became numb. The examination showed moderate wasting of the intrinsic hand muscles and the thenar eminences, and moderate wasting and weakness of the peroneal muscles and small foot muscles, with pes cavus and hammer toe formation. Ankle jerks were absent, and sensation was reduced to the wrists and ankles. She walked with a mild steppage gait.

Patient D. On examination, this 29-year-old female reported that she had highly arched feet since childhood, was unable to ice skate, and had slight difficulty walking on uneven ground with a tendency to trip. The examination showed slight wasting and weakness of intrinsic hand muscles, highly arched feet, and hammer toe formation but only a little weakness in ankle dorsiflexion and eversion. Ankle jerks were absent, and there was a mild impairment of sensation in her toes and soles. Her gait was normal.

Thus, the affected men and women developed symptoms and signs of a progressive, length-dependent neuropathy. Most males had clinical onset in the first decade, developed a significant gait disturbance in the second decade, with progression to the point of requiring aids, but did not become wheelchair bound. Women, by comparison, first noted symptoms toward the end of the second decade, and at every age, were much more mildly affected. Similarly, electrophysiological testing demonstrated that affected men had more axonal loss, including several who had an absent extensor digitorum brevis motor responses. Both men and women; however, had mild to moderate slowing of the peroneal motor response. Sensory nerve biopsies of 2 affected men (Patient A and Patient B) revealed evidence of demyelination and remyelination, as well as axonal degeneration and regeneration.{embed="pagecomponents/media_embed" entry_id="9677"}

Biological basis

Etiology and pathogenesis

CMT1X is caused by mutations in *GJB1*, the gene that encodes the gap junction protein connexin32 (Cx32).

In the 100 years following Herringham's paper, many workers reported other CMT1X kindreds from Europe and North America. Although the existence of X-linked kindreds with inherited neuropathy fell into dispute by 1980, their existence was confirmed by subsequent linkage studies. Recombination analyses in several large families refined the localization of CMT1X to an approximately 1.5 megabase interval in Xq13.1, where 3 genes previously had been mapped, including *GJB1*. Because mutations in genes expressed by myelinating Schwann cells were known to cause other inherited demyelinating neuropathies, Bergoffen and colleagues tested whether these candidate genes were expressed in normal rat peripheral nerves (Bergoffen et al 1993). *GJB1* was the only one expressed, and direct sequencing of *GJB1* in 8 families demonstrated 7 different mutations. Subsequent reports, largely from patients from Europe and North America, but also from Russia, Japan, China, Korea, and Turkey confirmed these findings. Many mutations have been reported more than once; some probably represent founder effects, whereas others may represent mutational hot spots.

Some CMT1X kindreds do not have mutations in the open reading frame. In these families, mutations might affect the promoter, splice sites, or the untranslated portions of the mRNA. In mammals, *GJB1* is composed of 2 exons and a large intron (6 to 8 kb). The second exon contains the entire open reading frame. Cx32 transcripts in peripheral nerves are initiated at an alternative promoter, termed P2, which is located close to the exon 2. Transcripts in the liver, brain, spinal cord, and pancreas, on the other hand, are initiated at the P1 and the P2 promoters. Several mutations are just proximal to the start site of transcription, likely affecting the EGR2 and SOX10 binding sites; these are important transcription factors for the development and maintenance of myelinating Schwann cells (Svaren and Meijer 2008). Other mutations affect the splicing of exons 1A and 2 (Murphy et al 2011), or abolish an internal ribosome entry site (-459C>T) in the 5' UTR, which is essential for the translation of Cx32 mRNA (Hudder and Werner 2000).

Gap junctions are intercellular channels, usually between adjacent cells, and are found in most tissues (Bruzzone et al 1996; Goodenough et al 1996). Intercellular gap junctions have been postulated to be involved in a number of processes, including metabolic cooperation, spatial buffering of potassium ions, intercellular synchronization, growth control, cellular differentiation, and pattern formation during development. The channels are composed of 2 apposed hemichannels (or connexons) that can form a contiguous pathway between the adjacent cells. Each connexon is composed of a hexamer of connexin molecules arranged around a central pore. All connexins are believed to have a similar structure (Maeda et al 2009).{embed="pagecomponents/media_embed" entry_id="9679"} In the transmembrane domains are alpha helixes; the first transmembrane domain forms the central pore. The channel diameter is too small to allow transfer of proteins and nucleic acids but large enough to allow the diffusion of ions and other small molecules (less than 1000 Da). The N-terminal domain is involved in the insertion of the nascent polypeptide chain into the endoplasmic reticulum, and, along with the first transmembrane domain, determines voltage gating. The extracellular loops regulate the connexon to connexon interactions, including heterotypic channel formation; each loop contains 3 cysteine residues (conserved among all connexins) that form essential intramolecular disulfide bonds. The intracellular loop and C-terminal domain regulate pH gating.

In keeping with the diversity of tissues with gap junctions, 21 different connexins have been found in mammals (Willecke et al 2002). Most connexins are expressed in more than one tissue and most tissues express more than one connexin. All connexins are highly homologous, indicating that their structure and function were conserved as they evolved from a common ancestral gene. The possible interactions of different connexins are potentially complex, as connexons may be composed of a single connexin (homomeric connexons), or they may be heteromeric. Furthermore, homomeric connexons can couple with homomeric connexons composed of the same connexin (homotypic junctions), with connexons composed of a different connexin (heterotypic junctions), or even with different combinations of heteromeric connexons. Not all combinations of hemichannels, however, can form heterotypic junctions.

Cx32 was the first connexin to be cloned and was named according to the predicted molecular mass of the protein, 32 kDa. It is highly conserved; the amino acid sequence of human Cx32 protein is 98% identical to those of the mouse and rat. Despite the broad expression pattern of Cx32, peripheral neuropathy is usually the sole clinical manifestation of *GJB1* mutations, although CNS abnormalities are associated with certain mutations. Why these other tissues are not affected is unclear. One reason may be the co-expression of other connexins, which could protect against the loss of Cx32. Myelinating Schwann cells in rodents express Cx29 (Altevogt et al 2002), whether human Schwann cells express Cx31.3, the human ortholog of Cx29, remains to be determined.

The *GJB1* mutations that cause CMT1X involve all portions of the Cx32 protein. Because mutations affect conserved regions, one might anticipate that they disrupt its function. The effects of some mutations can be inferred from the locations of the affected amino acids, as detailed above. For instance, there are naturally occurring mutations affecting all 6 cysteines of the extracellular loops; all of the corresponding mutants would be predicted to result in nonfunctional channels (Dahl et al 1992). Because the effects of individual mutations are difficult to predict, many mutations have been expressed in Xenopus oocytes. Many mutants do not form functional channels, although they probably do reach the cell membrane (Abrams et al 2000). In contrast, other mutants form gap junctions, but most of these have abnormal biophysical characteristics, including their incorporation into hemichannels. It is possible that some Cx32 mutants affect other connexins that are expressed by myelinating Schwann cells (Cx29) or oligodendrocytes (Cx29 and Cx47) (Altevogt et al 2002; Menichella et al 2003; Odermatt et al 2003). Dominant effects could result in a more severe phenotype, particularly in the central nervous system (see below).

In mammalian cells, many Cx32 mutants do not reach the cell surface (Yum et al 2002); these mutants cannot form functional gap junctions. Other mutants reach the cell surface and form gap junctional plaques. One reason for the

discrepancy in the cell surface localization of Cx32 mutants is the more stringent requirements in mammalian cells for protein trafficking; misfolded proteins are degraded in 2 distinct pathways, involving either proteasomes or lysosomes. Different Cx32 mutants exhibit different trafficking defects and differ in their sensitivity to drugs that block proteasomes and lysosomes (VanSlyke et al 2000). These findings fit the general theme that the molecular pathogenesis of intrinsic membrane proteins is related to abnormal trafficking of the mutant proteins. Finally, these results highlight the limitations of transfection analysis, which did not reveal any abnormality in trafficking or function of several mutants that cause CMT1X. Even expressing these mutants in myelinating Schwann cells has not revealed how some Cx32 mutants cause disease (Huang et al 2005).

Until *GJB1* mutations were found to cause CMT1X, little attention had been paid to the finding that myelin sheaths may contain gap junctions. Putative gap junctions were seen within paranodes and incisures by freeze fracture electron microscopy, exactly where Cx32 immunoreactivity is found (Bergoffen et al 1993; Meier et al 2004). Paranodes and incisures are regions of non-compact myelin in the myelin sheath and contain different intrinsic membrane proteins from those of compact myelin.{embed="pagecomponents/media_embed" entry_id="9680"} If Cx32 forms functional gap junctions in incisures and paranodes, then these could provide a direct pathway for the diffusion of ions and small molecules directly across the myelin sheath. For thick myelin sheaths, this direct radial pathway would be 1000 times shorter than the circumferential pathway through the Schwann cell cytoplasm. Thus, myelinating Schwann cells may use "reflexive" gap junctions (gap junctions of a cell onto itself) to compensate for long circumferential pathways for diffusion of small molecules and ions, inherent to their specialized geometry. If Cx32 mutants interrupt the function of these gap junctions, then this could damage myelinating Schwann cells and their axons, leading to demyelination as well as axonal loss.

Dye transfer studies, the standard way of demonstrating dye-coupling between cells, have demonstrated functional gap junctions in the myelin sheath (Balice-Gordon et al 1998). Living myelinated fibers were injected with dyes of differing molecular mass. Dyes of low molecular mass can pass from the outer (abaxonal) collar of Schwann cell cytoplasm to the inner (adaxonal) collar of cytoplasm, whereas high molecular mass dyes do not reach the adaxonal cytoplasm. Furthermore, pre-incubating the teased fibers in an agent known to uncouple gap junctions prevents low molecular mass dyes from diffusing into the cytoplasm adjacent to the axon. These results indicate that there is a gap junction-mediated pathway for diffusion of small molecules directly across the myelin sheath, probably located within incisures. This pathway did not appear to be disrupted in the myelinating Schwann cells from *Gjb1*-null mice, indicating that other connexins may compensate for the absence of Cx32. Cx31.3, the human ortholog of rodent Cx29, is a strong candidate, except that it does not appear to form functional channels (Ahn et al 2008; Sargiannidou et al 2008).

Given the large number and variety of *GJB1* mutations, the question arises whether different mutations cause different degrees of clinical involvement. This is clearly the case for mutations in *PMP22* and *MPZ* genes that encode other myelin proteins (Scherer and Wrabetz 2008). Different *PMP22* and *MPZ* mutations cause a wide range of phenotypes, ranging from mild (hereditary neuropathy with liability to pressure palsies) to severe (congenital hypomyelinating neuropathy or Dejerine-Sottas syndrome. In spite of earlier suggestions of a genotype-phenotype correlation (Deschenes et al 1997; Ionasescu 1998), a more thorough investigation indicates that many *GJB1* mutations cause a similar phenotype, equivalent to a null allele (Shy et al 2007). Thus, if a *GBJ1* mutation is found in a person with the typical clinical and electrophysiological picture of CMT1X, then it is likely the cause of their neuropathy, especially if the same mutation has been reported in another family. Not all *GJB1* mutations, however, cause CMT1X, as several synonymous and even nonsynonymous mutations are found more commonly than expected for the prevalence of CMT1X ExAC Browser Web site, including p.Phe235Cys, which was previously reported to cause a severe neuropathy (Liang et al 2005). Another missense mutation (p.Val170Ile) has been shown to be a benign polymorphism (Brozkova et al 2010).

GJB1 mutations cause 3 kinds of CNS manifestations (Abrams and Scherer 2012):

(1) Many mutations cause delayed brainstem auditory evoked responses, even in the absence of clinical involvement (Nicholson et al 1998). Visual and motor pathways may also be affected (Bähr et al 1999).

(2) Some mutations are associated with mild, fixed CNS findings such as extensor plantar responses or abnormal MRIs when asymptomatic (p.Trp3Gly, p.Trp24Cys, p.Met34Val, p.Ala39Val, p.Asn54His, p.Met93Val, p.Ser128Leu, p.Arg143Pro, p.Trp157Cys, p. Val170Phe, p.Asn175Ser). p.Asn54His is associated with persistent CNS dysfunction in 1 child who also had an abnormal brain MRI (Siskind et al 2009). p.Cys64Tyr was found in several members of a family who also had white matter changes on MRI, one of whom has an multiple sclerosis-like illness.

(3) Some mutations (p.Met1Ile, p.Arg22Gln, p.Val27Ala, p.Ile33Asn, p.Ala39Val, p.Phe51Leu, p.Asn54Ser, p.Thr55Ile, p.Cy60Tyr, p.Asp66Asn, p.Arg75Trp, p.Pro87Leu, p.Gln99_His100insGln, p.His100Gln, p.Glu102del, p.Trp132stop, p.Trp133fs, p.Val139Met, p.Arg142Trp, p.Arg142Gln, p.Leu156Arg, p.Arg164Trp, p.Arg164Gln, p.Cys168Tyr, p.Val177Ala, p.Arg183His, and p.Glu186stop) are associated dramatic, transient clinical and MRI abnormalities of CNS involvement, often initially diagnosed as ADEM or a stroke.

(4) One mutation, p.Pro58Ser, has been associated with spinocerebellar degeneration (Spira et al 1979; Caramins et al 2013).

(5) At least 4 different *GJB1* mutations (p.Val38Ala, p.Thr55Arg, p.Arg142Gln, and p.Thr191frameshift) have been associated with hearing loss, some of these also were found to have prolonged brainstem auditory evoked responses (Stojkovic et al 1999; Lee et al 2002; Karadima et al 2004); there may be others (Nicholson et al 1998; Hattori et al 2003). Males, and even females, can be affected in childhood.

Epidemiology"

Charcot-Marie-Tooth disease is a common genetic disease, with an estimated prevalence that ranges from 1/2500 to 1/8000 (Emery 1991). CMT1X is the second most common form of Charcot-Marie-Tooth disease, after CMT1A, accounting for 10% of all Charcot-Marie-Tooth disease patients (Fridman et al 2015).

Prevention

The manifestations of CMT1X cannot be prevented by any known measures. Selective prenatal testing can be done. Sperm selection is a theoretical possibility for affected men, as only the "X" sperm carry the mutant allele.

Differential diagnosis

Inherited neuropathy should be considered in the differential diagnosis of every patient who has a chronic, length-dependent neuropathy of unknown etiology. A clear family history and electrophysiological evidence of a chronic, length-dependent neuropathy are the hallmarks of all inherited neuropathies. Sporadic cases of CMT1X have been described, however, including ones caused by new mutations, so the absence of a family history does not exclude CMT1X (or any other inherited neuropathy). The following genetic, clinical, electrophysiological, and pathological features differentiate CMT1X from other forms of Charcot-Marie-Tooth disease.

A diagnosis of CMT1X should be considered for patients who appear to have CMT1, especially if the family history indicates that men are more affected than women and no male-to-male transmission is documented. The degree of slowing on electrophysiological testing helps to distinguish CMT1 from CMT1X, as forearm motor velocities in CMT1 (10 to 40 m/sec) are often slower than in CMT1X (30 to 40 m/sec). This so-called "intermediate slowing" is typical for affected men but is also seen in affected women (Nicholson and Nash 1993; Birouk et al 1998; Dubourg et al 2001; Shy et al 2007). The nerve biopsies from CMT1X patients show more axonal loss and “regenerated clusters” of myelinated axons and fewer "onion-bulbs" as opposed to CMT1A (Sander et al 1998; Hahn et al 2001; Vital et al 2001).

Distinguishing CMT1X from CMT2 or "dominant intermediate" forms of CMT is more problematic, especially in small kindreds in which the lack of male-to-male transmission in not evident. Further, the clinical phenotypes of CMT1X and CMT2 can be similar, and the ranges of motor nerve conduction velocities overlap. In spite of the difficulties separating the two, the notion that *GJB1* mutations can cause CMT2 is unfounded. Rather, *GJB1* mutations cause demyelination that is compounded by axonal loss, whereas in CMT2 axonal loss is probably the fundamental pathological alteration.

Finally, it should be emphasized that atypical cases of CMT1X have also been described, largely owing to availability of genetic testing. CMT1X can affect young women and children of either sex. *GJB1* mutations have been found in patients with suspected inflammatory demyelinating neuropathies not responding to treatment (Michell et al 2009). Hearing loss and abnormalities in the central nervous system have also been described. In particular, stroke-like episodes of CNS dysfunction that are accompanied by MRI abnormalities have been described (Abrams and Scherer 2012). These episodes appear to be associated with a subset of *GJB1* mutations, and may be brought on physical exertion or a change in altitude.

Diagnostic workup

A family history of neuropathy and a physical exam that reveals features of a length-dependent peripheral neuropathy are strongly suggestive of an inherited neuropathy. Electrophysiological evaluation of multiple peripheral nerves along with electromyography will confirm whether the patient has a length-dependent neuropathy, and should also establish whether this is associated with slow (less than 30 m/sec), intermediate (30 to 40 m/sec), or normal (greater than 45 m/sec) motor conduction velocities in the arms. Symmetrical slowing indicates an inherited demyelinating neuropathy; asymmetrical slowing is characteristic of an acquired, demyelinating neuropathy. In CMT1X, however, the nerve conduction velocities are less uniform than in other forms of CMT1 (Gutierrez et al 2000; Lewis et al 2000), to the point that some patients were treated (unsuccessfully) for CIDP (Michell et al 2009). The cerebrospinal fluid from CMT1X patients has not been systematically characterized, but there are reports of mild elevations (less than 100 mg/dl), which may serve to distinguish CMT1X from chronic, acquired demyelinating neuropathies.

Patients who are suspected of having a genetic neuropathy with slow or intermediate motor conduction velocities should be advised that this could be a genetic neuropathy and that genetic testing is available. It would be reasonable to refer the patient to a neurologist who specializes in neuromuscular diseases or a genetic counselor who is familiar with Charcot-Marie-Tooth disease. After the genetic testing is explained, blood samples can be sent for testing. For CMT1X, the entire open reading frame of the *GJB1* gene should sequenced. If no mutations are found and CMT1X is strongly suspected, then the promoter and 5' untranslated region could be sequenced. Updated information on the availability of genetic testing can be found on the GeneTests Web site.

A nerve biopsy is not required to diagnose CMT1X.

Management

The National Institutes of Health Web site states, "There is no cure or specific treatment for Charcot-Marie-Tooth disease. Proper foot care including custom-made shoes and leg braces may minimize discomfort and increase function. Physical therapy and moderate activity are often recommended to maintain muscle strength and endurance. For some patients, surgery may be beneficial." The management issues are chiefly related to the orthopedic complications of the disease (Parry 1995). These include the well known foot deformities common to all types of Charcot-Marie-Tooth disease: pes cavus, varus, callosities on the lateral foot borders, and "hammer toes," which can compromise ambulation and even require surgical intervention. Ankle instability can be treated with high-top shoes or boots or orthoses, and foot drop can be treated with braces. Scoliosis has been noted in more severely affected patients, but the literature does not indicate that CMT1X patients typically need intervention (Horacek et al 2007). Physical therapy, especially stretching for contractures, is advocated, and splinting, specific exercises, adaptive devices, and surgery may help maintain hand function.

Special considerations

Pregnancy

Women with CMT1X are fertile. Pregnancy, labor, and delivery have not been reported to alter the disease.

Anesthesia

There is no specific information available about anesthesia and CMT1X. Although there are theoretical reasons for avoiding depolarizing neuromuscular agents such as succinylcholine during anesthesia because denervated muscle fibers might release potassium, thereby causing hyperkalemia, this has not been observed in patients with CMT1 (Antognini 1992). Patients with CMT1 may have increased sensitivity to thiopental, a drug widely used during the induction of anesthesia (Kotani et al 1996), and vecuronium, a neuromuscular blocker (Pogson et al 2000).

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**References especially recommended by the author or editor for general reading.

ICD and OMIM codes

ICD codes

ICD-9:
Hereditary neuropathy :356
Charcot-Marie-Tooth: 356.1

ICD-10:
Hereditary neuropathy :G60.1
Charcot-Marie-Tooth: G60.0

OMIM numbers

Gap junction protein, beta-1, 32 kD (connexin32): *304040
Charcot-Marie-Tooth neuropathy, X-linked-1, dominant: #302800

Profile

Age range of presentation

0-01 month
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

Sex preponderance

male=female

Family history

family history may be obtained
family history typical

Heredity

X-linked dominant

Population groups selectively affected

none selectively affected

Occupation groups selectively affected

none selectively affected

Differential diagnosis list

Charcot-Marie-Tooth disease type 1A
Charcot-Marie-Tooth disease type 1B
Charcot-Marie-Tooth disease type 1C
Charcot-Marie-Tooth disease type 1D
Charcot-Marie-Tooth disease type 2
Chronic inflammatory demyelinating polyneuropathy

Associated disorders

Other topics to consider

Charcot-Marie-Tooth disease type 1A
Charcot-Marie-Tooth disease type 1B
Charcot-Marie-Tooth disease: CMT2, CMT4, and others
Hereditary neuropathy with predisposition to pressure palsy
Introduction to peripheral neuropathies
Molecular diagnosis of neurogenetic disorders