The Patients' Guide to

Charcot-Marie-Tooth Disorders

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Foreword

Each chapter in this Patients' Guide was authored by an expert on one specific topic related to Charcot-Marie-Tooth disorders.

We thank them both for their expertise and for the generous gift of their time and effort in producing this source of information about CMT for patients, families and medical professionals.

Since each author was working independently, it was inevitable that there would be some repetition of general information about CMT. We apologize for that, but we also chose to retain each author's full content for the benefit of those people who only read selected chapters.

We would also like to thank the Pennsylvania Department of Health whose funding made this publication possible.

Last but not least, we owe special thanks to Dr. Michael Shy, head of the CMT Clinic at Wayne State University and the Chairman of our Medical Advisory Board. In addition to contributing a chapter, Dr. Shy reviewed the other chapters for scientific and medical accuracy.

Any errors you may find, however, are not his alone. All of us at the CMTA who had a hand in proofing and formatting the guide are responsible.

We hope you find this guide as invaluable as we intended it to be.

The CMTA

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Historical Perspective and Overview

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Hereditary peripheral neuropathies were described in 1886 by Tooth in the United Kingdom and by Charcot and Marie in France; hence, the disorders are known as Charcot-Marie-Tooth (CMT) disease. A decade earlier, Eichhorst (1873) published a 6-generation pedigree and Friedreich (1873) presented a clinicopathological study. Salient features recognized by Charcot, Marie and Tooth included heredity and progressiveness, distal limb weakness, maximal in the legs (peroneal muscular atrophy), childhood or adolescent onset, foot deformity, areflexia and variable distal sensory loss.

The heterogeneous nature and different forms of inheritance of the condition were soon appreciated. In 1889, Herringham reported a family with selectively affected male members. In 1893, Dejerine and

Sottas described a more severe, infantile-onset disease with an intriguing type of morphologic change—the onion bulb. Dejerine-Sottas disease is characterized by nerve fibers that are surrounded by concentrically proliferated cells that resemble a cross-section of an onion. Onion bulbs were later recognized in many inherited and acquired neuropathies. Roussy and Levy (1926) described familial cases of tremor, claw foot, ataxia and areflexia. While central nervous system and non-neural structure involvement has been reported in some families (with specific gene mutations), it is important to emphasize the dominance of peripheral nervous system involvement in CMT. Contrast CMT's peripheral system involvement to the combined peripheral and central nervous system involvement seen in metabolic and neurodegenerative disorders, such as leukodystrophies, spinocerebellar atrophy and mitochondropathies.

The advent of modern neurophysiologic testing and advances in peripheral nerve pathology in the late 1960s led to the first semblance of order in CMT classification. Dyck and Lambert showed that some patients with a clinical diagnosis of peroneal muscular atrophy or CMT disease had a purely motor syndrome, now generally designated as distal hereditary motor neuropathy or distal spinal muscular atrophy. In other patients, sensory axons were involved, leading to the naming of these forms of CMT as hereditary motor and sensory neuropathy (HMSN). Dyck and Lambert's major contribution were two landmark publications detailing the genetic and clinical characteristics of more than 200 patients, which showed that clinically identical CMT patients could be separated into two broad groups based on electrophysiologic and pathologic findings and that these groupings were consistent within families.

The first group, HMSN I (CMT1), is characterized by severely reduced nerve conduction velocities (NCVs) and by extensive demyelinating and hypertrophic changes (onion bulbs) on nerve biopsy. In the second group, HMSN II (CMT2), NCVs were normal or only mildly reduced and nerve biopsy showed loss of axons with little

demyelination. As a dividing value between both forms, NCVs of 38 m/s are used by some and NCVs of 42 m/s by others. NCVs in CMT1 are typically uniformly slow along individual nerves and between different nerves of an individual patient, which distinguishes CMT1 from acquired demyelinating neuropathies, such as acute or chronic inflammatory demyelinating polyneuropathies. Both CMT1 and CMT2 were shown to be genetically heterogeneous with autosomal dominant, recessive or X-linked inheritance. Roussy-Levy syndrome was shown to be a variant of CMT1 and distinct from Friedreich's ataxia.

In addition to the distinction of CMT1 and CMT2, overlap syndromes have long been recognized in both individuals and families with median motor NCVs of 25-45m/s, and have been called intermediate conduction velocity CMT or intermediate CMT (DI-CMT). The distinction between CMT1 and CMT2 was further challenged by reports of relatively normal NCVs suggestive of CMT2 in younger members of a family, whereas older relatives had severe slowing of NCVs, which is consistent with CMT1.

The subsequent splitting of CMT disease into multiple genetic entities was not an idle academic exercise. The identification of particular clinical syndromes with differing patterns of inheritance was vital for accurate genetic counseling, and it paved the way for the spectacular advances in the molecular genetics of CMT since the early 1990s. Our appreciation of the heterogeneity of CMT deepened further when linkage studies demonstrated *CMT1* loci on chromosome 1 and 17, and soon thereafter, disease mutations in the *PMP22* and *MPZ* genes. To date, more than 50 CMT loci and mutations in over 20 genes have been identified for different subtypes of CMT1, CMT2, DI-CMT, X-linked and autosomal recessive forms.

CMT may be the most common hereditary neurological disease. In the United States, it affects approximately 150,000 people. An exhaustive study from Norway indicated a prevalence of 3.6 cases

per 10,000 people. A worldwide meta-analysis estimated a prevalence of 1 case in 10,000 people. A recent Japanese epidemiologic study demonstrated a prevalence of 10.8 cases per 100,000 people. Approximately 66 percent of patients diagnosed with CMT have CMT1, 20 percent have CMT2 and 15 percent have the X-linked form. Autosomal recessive forms of CMT are rare; several recessive forms have only been found in three or fewer families, often in small ethnic groups.

Correctly diagnosing CMT disease is important to avoid intercurrent medical problems (medical problems that arise from the occurrence of a disease that modifies the course of another disease) or medical interventions (such as a drug therapy or surgery) that may result in superimposed systemic or focal neuropathies. Intercurrent medical problems include diabetes mellitus, hypothyroidism, vitamin deficiencies and carpal tunnel syndrome; interventions that may cause medical problems in CMT patients include prolonged immobilization of limbs during surgery and neurotoxic drugs. For example, if drugs such as platinum compounds or vincristine are given to CMT patients, severe toxic neuropathies may occur.

Most patients with the disease remain ambulant and have an active and productive life. Proper lifelong orthopedic attention can often prevent the development of serious foot and spinal deformity. Orthotic devices or corrective surgery may result in a substantial functional benefit. Patients with severe sensory loss must be educated about proper foot care so that foot injuries do not cause chronic foot ulceration or other foot problems.

This book addresses the diagnosis and management of patients with CMT disease. Our understanding of the disease has advanced considerably in the past few years and this knowledge can be translated into improved health care.

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Clinical Features of Charcot-Marie-Tooth Syndrome

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First description of CMT

Neurologists in the second half of 19th century took a special interest in neurological disorders characterized by muscle wasting, which is also called muscular atrophy. In 1886, the famous neurologist Jean-Martin Charcot and his co-worker, Pierre Marie, at the prestigious Salpétrière Hospital in Paris, France, described a few individuals with a special form of muscle atrophy. (Howard Henry Tooth in Oxford, England independently made a similar observation.) In their original report in the *Revu Neurologique,* Charcot and Marie described the disorder as "a peculiar form of muscle atrophy," starting with weakness and atrophy in the feet and later on involving the hands; sensory symptoms were usually present, but never prominent, and tendon reflexes were absent or diminished. They also noticed that some affected individuals had relatives who were similarly affected. These characteristics are still the cardinal features of what is now known as Charcot-Marie-Tooth syndrome. A few years later, Hoffmann noted that some affected individuals had enlarged nerves that were palpable or even visible under the skin. Therefore, some older publications mention "Charcot-Marie-Tooth-Hoffmann syndrome". However, after some fierce debates in the medical literature of that time, it was decided that this contribution did not merit the addition of Hoffmann's name.

These giants of early neurology were extremely skillful clinicians and to fully appreciate their brilliant achievement, it should be remembered that they hardly had any tools to document the disorder in their patients. The examinations we are currently using to diagnose CMT were introduced much later in clinical practice: the earliest reports of EMG abnormalities in CMT stem from the early 1950s; advanced microscopic examination of nerve biopsy specimens was introduced in the 1960s and molecular genetic diagnosis only become possible in the 1990s. Also, the laws of heredity described by Gregor Mendel were largely forgotten and only rediscovered in the beginning of the 20th century.

In addition, muscle wasting was still poorly understood in 1886. Initially Charcot and Marie erroneously hypothesized that the pathological process resided in the spinal cord, while Tooth correctly localized the disease process in peripheral nerves.

Core features of classical CMT

Although based on a very small number of patients, the description of the clinical symptoms by Charcot, Marie and Tooth was so complete that nothing essential has been added until quite recently, and we refer to Charcot, Marie and Tooth's description as *classical CMT*. We now know that CMT is a peripheral neuropathy and that the underlying biological problem is the inability to maintain the tips of long nerves (nerves that may be as long as 1 meter in length) in optimal condition. This easily explains why symptoms and signs, both motor and sensory, start at the far end of the extremities (that is, the toes and fingers). Symptoms are, in general, fairly symmetrical, although asymmetry is sometimes observed. The following sections detail the distinct features of CMT.

Weakness

Distribution and evolution of weakness in classical CMT is so stereotyped that it is the key diagnostic feature. The first striking sign

is weakness of the extensor muscles of the big toe, which are the muscles that lift the big toe. Later in the course of the disorder, the muscles that lift and turn the foot outwards become progressively weaker. Consequently, neurologists will test whether a person can walk on heels to determine if there is weakness in these muscles; the inability to walk on heels is sometimes the only sign detectable in early stages of the disease or in individuals who are minimally affected. Sometimes weakness remains confined to these muscle groups, but in most affected individuals, other muscle groups, such as the plantar flexors of the foot and the muscles that turn the foot inwards, become progressively weaker. In severely affected individuals, feet can become completely paralyzed, while strength in thigh muscles usually remains intact. After a delay of several years, weakness also starts in fingers. In most affected individuals, extensors and flexors of the wrist and upper arm muscles remain strong.

Muscle wasting

Muscles become weak and lose bulk; small muscles may even disappear. This phenomenon is first seen in small feet muscles. As a result, tendons at the sole and back of the feet look more prominent. Lower leg muscles grow thinner, and sometimes the lower part of the thigh also becomes thinner. Legs of affected individuals are therefore sometimes described as “stork legs” or are compared to an inverted champagne bottle. When hand muscles become weak, they also become atrophic. This is often striking at the first interosseus muscle (the muscle between the thumb and index finger) and the muscles at the base of the thumb.

Sensory symptoms

Neurologists tend to classify sensory symptoms as positive or negative. Positive symptoms comprise pain and pins-and-needles sensations. Negative symptoms refer to loss of sensation. Positive symptoms are often a disturbing feature of acquired neuropathies, such as diabetic neuropathy. Fortunately, they are much less

common in CMT. In fact, as already noted by Charcot and Marie, sensory symptoms are seldom prominent and, if present, result in loss or diminishment of sensation. The abnormalities can be subtle and require careful clinical examination or EMG testing to be detected. A feared complication of diabetic neuropathy is poorly healing ulcers that initially go unnoticed because of loss of pain sensation. These ulcers may become infected, eventually leading to infections of the bones and necessitating amputations of parts of the limbs. Although this complication has been described in classical CMT, it is very rare and can be prevented by good foot care and visual inspection of the feet by affected individuals who have unusually pronounced “loss of pain” sensation.

Pain

Although CMT is often considered by doctors to be a painless disorder, surveys based on questionnaires filled out by affected individuals always show that pain is common in CMT. Pains, however, have different origins and careful history taking and clinical examination are needed to elucidate the exact source and to initiate appropriate treatment. As already mentioned, neuropathic pain directly attributable to CMT is rare. It presents as a burning sensation, needle-and-pins, or a feeling of tightness around ankles; more often, pains are secondary and include aching pains in over-worked muscles. Affected individuals know that the only method to prevent this, at least to some extent, is to break down physical activities into smaller units and to take short rests in between. Other pains result from the altered walking pattern that leads to increased strain on tendons and joints—particularly knees, ankles, hips and the lower back. Pressure points at the soles of the feet and toes may result in callus formation and pain. Occasionally, hip displacement or patella luxation (kneecap dislocation) may be the cause. As a rule, pain should not be accepted as intrinsic to CMT because correct treatment of secondary pain is often possible providing that the source of the pain is identified.

Cold legs

A sensation of intense coldness is a common complaint in peripheral neuropathies in general, and thus, also in CMT. Feet and lower legs often show a red/purplish discoloration. This is probably due to some involvement of the autonomic nervous system (nerves that regulate involuntary control of cardiac muscle, organ smooth muscle and glands). Apart from discomfort and the aesthetic aspects, some affected individuals are concerned that this phenomenon is an indication of circulatory problems and may lead to ulcers. They often compare their symptoms to diabetic neuropathy, where such complications are common. However in CMT, these vascular complications are extremely rare.

Skeletal deformities

Deformities of feet are a common problem in CMT. They tend to be more severe in individuals with an early onset of the disease. Deformities result from an imbalance between extensor and flexor muscles; the impact of the imbalance is greater when bones are still malleable. The most classical abnormality is *pes cavus* or hollow foot (distinguished by high arches). However, some affected individuals have flat feet. Hammertoes often go together with hollow feet. Consequently, finding shoes that fit well is often difficult for affected individuals. Foot deformities add to walking difficulties and altered architecture of the foot may create pressure points that result in callus formation and pain. Spine deformities in the form of scoliosis can occur in classical CMT. Orthopedic problems such as hip displacement and patella luxation are more common in CMT than in the general population. A common problem is shortening of the Achilles tendon. Collagen fibers in tendons are rapidly degraded and replaced; therefore, tendons adapt their length to the position that is commonly taken during the night or large parts of the day. With increasing weakness of the extensor muscles, feet drop and Achilles tendons shorten. Individuals with shortened Achilles tendons walk on the tips of the toes, which adds to instability.

Onset age, initial symptoms and progression

Age of symptom onset is usually within the first or second decade of life. Onset, however, is so insidious that it is often difficult to pin-point the exact beginning. We have noticed that in large families, grandmothers may be the experts who can spot the earliest signs of the disease—even within the first year of life. With hindsight, most affected individuals remember that as a child, they fell more easily, were unable to run as fast as children of the same age, were less skilled in sports, walked on toes or had always problems finding well-fitting shoes because of foot deformities. Unfortunately, children affected with CMT may be teased because of their unusual gait, considered uncoordinated in sports, or regarded as slovenly because of poor handwriting. Other affected youths can engage in activities without any problems. Occasionally, affected individuals develop first symptoms later in life, such as in their 40s or 50s.

CMT always progresses slowly; in fact, recent investigators needed to devote considerable time and effort to develop a test battery that can objectively measure subtle changes over a limited period of 1 year. Sudden exacerbations never occur and warrant investigation for concomitant disease (a different disease occurring at the same time as CMT).

Individual symptoms of CMT add up to functional disabilities that we will discuss here in more detail.

Walking difficulties

Muscle weakness and foot deformities lead to progressive walking difficulties. Because of drop feet, affected individuals have to lift their knees higher to detach the tip of the feet from the floor and they tend to sway more in the hips. When placing the feet on the ground, the tips of the feet hit the ground first, producing the typical slapping sound of drop-foot. This characteristic gait is sometimes disrespectfully referred to as “duck walk”. Even severely affected individuals with a complete paralysis of all foot

muscles are able to walk independently, indicating that preserved strength of thigh muscles is the crucial factor. As previously mentioned, thigh muscles remain strong in classical CMT. To some extent, this may be reassuring for mildly affected individuals who fear that they will eventually lose the ability to walk.

It is sometimes overlooked that sensory abnormalities may contribute considerably to walking difficulties. Balance is highly dependent on sensory information from feet and ankle joints. In bright daylight and in a quiet environment, affected individuals will unconsciously respond to visual clues and compensate for this loss of proprioception (awareness of the position of one's limbs). In the dark, this compensation breaks down and affected individuals become unstable.

The walking pattern of some affected individuals demands much more energy, leading to earlier fatigability. In a normal walking pattern, taking one step prepares you to take the next step, which results in highly efficient energy consumption focused on forward movement. In the CMT walking pattern, a lot of energy is invested in upward movement of the feet and knees and the smooth transfer of energy from one step to the other aimed at forward movement is lost.

Imbalance

Affected individuals not only experience walking difficulties, but they also often have problems standing still for a long period of time.

Upper limb disabilities

Weakness and sensory loss in the hands may lead to loss of dexterity. Handwriting or handling of small objects may become

difficult. However, hand function is never lost in classical CMT.

Variability

Although the combination of symptoms and disabilities in classical CMT are fairly constant, the degree of severity is variable between individuals. Affected individuals within the same family (including identical twins) may have considerable differences in symptom severity. It is not uncommon to find in the same family a child with prominent walking difficulties and hand weakness rendering him incapable of handling scissors while the child's 70-year-old grandparent is almost asymptomatic. These differences make it impossible to make accurate individual prognoses. However, some general predictions can be made.

Prognosis

Although appreciation of disability is a very subjective matter, classical CMT is usually described as "mild" or "moderately severe". The overwhelming majority of individuals with classical CMT remain ambulatory during all their lives. The impact of CMT is variable and depends on many factors, such as symptom severity, individual coping strategies, professional activities and the level of support from family and friends. CMT often interferes with professional activities, especially when the activities are physically demanding; this should be taken into account when counseling young people. However, affected individuals who are able to perform strenuous labor (such as working as coal miners and postmen) until normal retirement age are not uncommon. Importantly, individuals with CMT have a normal life expectancy. This may be a consolation for affected individuals, but this information is also crucial when dealing with an affected individual's insurance company.

Complications in classical CMT

Complications are rare in classical CMT. Medication can worsen CMT; common sense dictates that doctors should be cautious when

prescribing drugs with the potential of affecting the peripheral nervous system. However, complications have only been documented with Vincristine, a drug used in cancer treatment. There have been several reports of people who developed severe weakness leading to inability to walk or stand within days or weeks after administration of this drug. In several instances, it was unknown that the persons had CMT (particularly in the case of young children treated for leukemia) until this complication occurred. Very rarely, respiratory problems occur in classical CMT. This can be due to palsy of the phrenic nerve that innervates the diaphragm, but we have also seen transient respiratory failure in an affected individual who was in a very debilitating condition due to malnutrition. Treatment led to full recovery.

As already mentioned, loss of pain sensation may lead to skin ulcers at pressure points in the feet. This complication, however, is rare in classical CMT.

Additional features of CMT

Unfortunately, CMT does not protect against other disorders, and as in all chronic disorders, affected individuals and their physicians face the dilemma to accept additional symptoms as part of the CMT phenotype or to start investigations for concomitant disease. This problem can only be solved by doctors with experience in treating CMT. It is obvious that occasionally an affected individual will develop a common disorder, such as migraine or epilepsy, but this is purely co-incidental. We will here discuss some symptoms that may be causally related to CMT. These additional symptoms can be present in a single person in a family, but it may also run in the family, which offers important clues toward the correct diagnosis of a particular CMT subtype. It should be stressed that these peculiar CMT subtypes are very rare.

Hearing impairment
Hearing impairment is a common problem, especially in the elderly. Therefore, co-occurrence is often coincidental and warrants further investigations. However, hearing impairment occurs more frequently in individuals affected by CMT, indicating that the acoustic nerve may be affected by the disease process. Sometimes hearing impairment occurs at a young age and is then a constant finding associated with particular CMT variants such as CMT-Lom, a CMT variant described in an ethnic group known as the Roma.

Eye problems
Visual problems are rarely due to CMT. However, a few affected individuals with a particular form of CMT due to mitofusin protein mutations noted a sudden drop in visual acuity. These individuals usually showed subsequent partial or complete recovery. Cataract and glaucoma are common eye disorders, especially in the elderly. In rare forms of CMT, they are part of the phenotype, but occur at a much younger age than in the general population.

Hoarseness
Vocal cord paralysis is a very rare complication of classical CMT. It is, however, an invariant feature of some CMT subtypes. In these subtypes, hoarseness may be the presenting symptom (the symptom that first leads a patient to see a doctor).

Scoliosis
Scoliosis is often seen in affected individuals with an early age of onset. In these individuals, weakness predominates and the degree of scoliosis is proportionate to weakness. However, in rare CMT variants, scoliosis may be the presenting symptom and is then disproportionate to weakness.

Facial muscles and swallowing problems
Weakness in facial muscles and the presence of swallowing problems occur very rarely in CMT.

Lancinating pains

Lancinating pain (stabbing or piercing pain) is rare in individuals affected by CMT. If present, it may orient towards specific subtypes such as hereditary sensory neuropathy type I or specific mutations in the *Myelin Protein Zero* gene.

Spasticity

Spasticity, the continuous contraction of muscles, results in walking difficulties that differ from the characteristic CMT gait pattern. Spasticity leads to “scissor” gait and can be detected by brisk reflexes and sometimes abnormal reflexes such as the Babinski reflex. (If the sole of the foot is stimulated on the outside edge and the big toe elevates as a result, it is potentially an indicator of neurological problems.) Spasticity always points to involvement of the central nervous system (that is, the brain and spinal cord), and only occurs in atypical forms of CMT, where it can be an invariant part of the clinical presentation. If there is any doubt, additional imaging examinations are crucial to rule out compression of the spinal cord.

Initial or predominant hand involvement

In contrast to classical CMT, weakness and atrophy may start and predominate in the hands. This peculiar distribution may point to special CMT variants caused by mutations in specific genes.

Features not associated with CMT

In this section we will briefly discuss features that are absent or only rarely associated with CMT. Still, they are important because they often are a major concern to affected individuals who, in our experience, are often afraid to bring them up at an outpatient consultation.

Memory, intelligence, personality problems

Cognitive functions remain spared in CMT, which underlines that CMT is a disorder of the peripheral nervous system. This part of the

nervous system is not involved in processing of these higher functions.

Cardiac involvement

A priori concerns (concerns that have not been validated by research) about cardiac involvement in CMT may at first appear fully justified. In CMT, muscles undergo atrophy and the heart is, of course, an important muscle. In addition, nerves are involved in the electric wiring of the heart. Nonetheless, while cardiac problems are a major concern in muscle disorders, cardiac involvement does not occur in CMT. This is why we can confidently state that life expectancy in classical CMT does not differ from the general population.

Respiratory problems

Respiratory failure is very rare in CMT and occurs only in severely affected individuals who usually have a very early age of onset and become wheel-chair dependent in the first or second decade of life. Absence of respiratory problems is reflected in normal life expectancy.

Incontinency, impotence

Although incontinence and impotence are frequent complications in diabetic neuropathy, the most common acquired neuropathy, they are generally considered not to be part of the CMT phenotype. One study surveying a group of individuals affected by CMT reported a slight increase in impotence, but this small survey does not allow firm conclusions.

Unusual forms of CMT

After reviewing all common and rare features of classical CMT, we are now fully armored to tackle the problem of unusual forms of CMT. “Unusual forms of CMT” is, in fact, a contradiction in itself. The unusual forms have some core CMT features, but deviate in other aspects so far from the original description by Charcot, Marie and

Tooth that the CMT designation can be questioned. In fact, shortly after the seminal description of the classical CMT phenotype, affected individuals with unusual features were reported. This resulted in the introduction of novel syndromes named after their "discoverers," such as Dejerine-Sottas (DSS) and Roussy-Levy syndrome. Some of these new entities faded, while others, such as DSS, survived in one form or another, although it is often difficult to reconstruct exactly what these pioneering neurologists described more than a century ago. For this reason, Dyck introduced more descriptive terminologies, such as hereditary motor and sensory neuropathies (HMSN), distal hereditary motor neuropathies (HMN or distal HMN) and hereditary sensory and autonomic neuropathies (HSN or HSAN).

Dejerine-Sottas syndrome

This designation is sometimes used to describe individuals with a severe, early onset CMT phenotype. They develop symptoms by ages 5 to 10 years and often become wheelchair dependent during the first or second decade of life. Affected individuals are more prone to develop severe scoliosis and respiratory insufficiency. Recent molecular genetic studies have shown that DSS can result from mutations in the same genes that are associated with classical CMT.

Congenital hypomyelination

Congenital hypomyelination is the most severe form of inherited peripheral neuropathies. Symptoms are present from birth. Infants have problems with suckling and breathing. If these children survive, they have severely delayed motor milestones and show severe disabilities. Although the clinical features of congenital hypomyelination differ widely from CMT, both disorders are often discussed in the same context since they are biologically related; particular mutations in the genes associated with classical CMT can result in congenital hypomyelination.

Hereditary neuropathy with liability to pressure palsies (HNPP)
This intriguing disorder is characterized by single or recurrent episodes of painless palsies limited to individual nerve trunks. These palsies are often provoked by pressure or long lasting repetitive movements. Recovery is usually good. Occasionally individuals with HNPP develop a more chronic neuropathy without overt episodes of palsies. Although classical HNPP hardly resembles CMT, both conditions are often discussed together because they involve a chromosomal rearrangement of the gene for *PMP22.* A duplication of this gene results in CMT1A, the most common form of CMT, while a deletion underlies HNPP.

Hereditary motor neuropathies
This group of disorders present as classical CMT, but symptoms are confined to the motor portion of the peripheral nervous system.

Hereditary sensory neuropathies
In this group of inherited neuropathies, sensory symptoms predominate or are exclusively present. These individuals should take extreme care to prevent development of ulcers at pressure points at the feet. These ulcers go unnoticed due to lack of pain sensation. Skin infection can spread to underlying bone, leading to osteomyelitis (infection of the bone). Even with currently available antibiotics, amputations of distal parts of limbs can not always be avoided.

Conclusion

This overview of clinical features of CMT may erroneously suggest that every affected individual is at risk to develop all sorts of symptoms and complications. In reality, the majority of affected individuals have the classical CMT phenotype. However, for the sake of completeness we also discussed rare presentations of CMT and related disorders. In clinical practice we always start to compare features in a newly diagnosed individual with the classical CMT

phenotype. Then the questions arise: are there additional symptoms and do they relate to CMT or are they coincidental and warrant further investigation? The presence of additional or unusual features may orient towards specific CMT subtypes or related disorders. In an ever increasing number of these rare variants, clinical diagnosis can be confirmed by molecular genetic testing, although it may be difficult to get these tests done because most of the analyses for rare variants are performed in research labs. Whether it still makes sense to use the eponym “Charcot-Marie-Tooth” for such a bewildering variety of inherited peripheral neuropathies can be debated. However, many neurologists and patient organizations continue to use “CMT,” which honors the contributions of these great pioneers of modern neurology.

Acknowledgement:

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Electrodiagnostic Evaluation

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Introduction

The electrodiagnostic evaluation, which comprises nerve conduction studies (NCS) and needle electromyography (EMG), is a key component of the clinical evaluation of people suspected to have CMT. It is also, unfortunately, probably the least popular aspect of the diagnostic evaluation. This section will describe the reasons why the studies are performed, the techniques used and the information obtained from the studies. It is intended to provide information to patients so that the procedure is more understandable and less intimidating.

The role that electrodiagnostic studies play in the evaluation

Electrodiagnostic studies provide physiologic information about how the nerves are functioning. In particular, NCS can determine if:

- the disorder involves only the motor nerves, only the sensory nerves, or both
- the nerves are conducting signals at normal or abnormally slow velocities
- slow velocities occur in all nerves and nerve segments or only in specific regions
- there has been a significant loss of sensory or motor nerve fibers

The EMG can show if there has been loss of motor nerve fibers and can demonstrate the distribution of loss. In addition, it can determine if the weakness is due to muscle disease, rather than nerve disease.

The information gained from an electrodiagnostic evaluation plays a crucial role in the clinician's efforts to make a differential diagnosis; the results can confirm if the patient has peripheral neuropathy and whether the pattern is consistent with that seen in CMT. It is the major determinant in differentiating CMT1 from CMT2, and the information can point to the intermediate form of CMT, as well. Electrodiagnostic evaluation also assists in determining the severity of CMT.

What happens during the study

There is no specific preparation required prior to the examination. One should not, however, use any skin creams on the arms or legs because this makes it difficult to keep the electrodes in place.

Electrodiagnostic evaluations pose essentially no risk to the patient. Nevertheless, precautions are taken with patients who are taking anti-coagulants (blood thinners) or who have cardiac pacemakers, defibrillators or other implantable electromagnetic devices. Such patients can still undergo the studies, however.

Because nerve conduction velocities are slowed by cold temperature, it is important that a relatively warm limb temperature be maintained. Therefore, the technician may warm the patient's hands or feet with warm soaks, heated towels or other warming devices.

The motor nerve conduction studies consist of electrical stimulation of the nerves with surface probes placed over the nerves. The stimulus is of very short duration and very little current is actually given. The stimulus intensity is increased until a maximal motor response is obtained. The responses are recorded with two surface electrodes

(sticky pads), one placed over the muscle belly and the other 2-3 centimeters away on the tendon (Figure 1). The stimulus is a bit uncomfortable and varies from a sensation similar to static electricity to a mild electric shock. The discomfort lasts a fraction of a second and there is no residual pain. The stimulus intensity varies depending on how far beneath the skin surface the nerve is and the excitability of the nerve. Unfortunately, some types of CMT have less excitable nerves, which require stronger stimulus intensities and more discomfort.

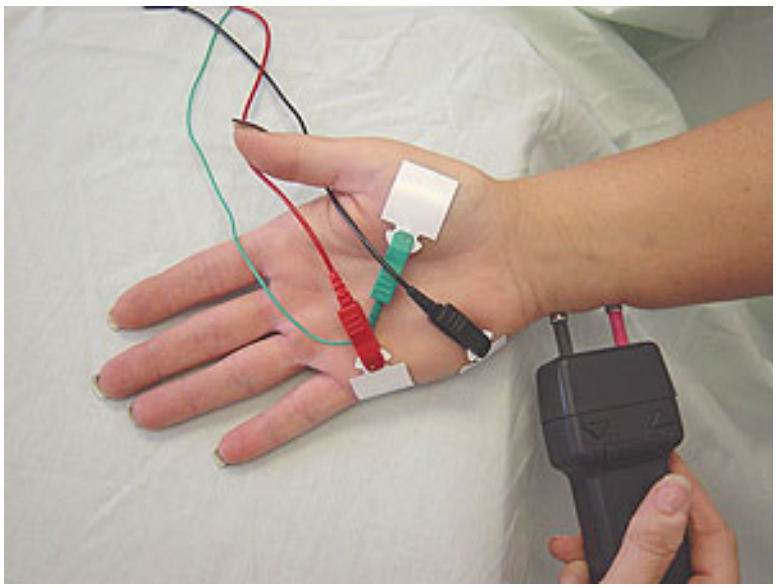

Figure. 1. Motor nerve conduction study of the ulnar nerve, stimulating at the wrist. The green electrode connects to the ground, the black recording electrode is over the muscle belly, and the red electrode is the reference.

The motor nerve conduction studies require stimulating the nerve at two sites. For the leg, this is usually at the ankle and near the knee. For the arm, this is usually at the wrist and near the elbow. For some nerves (the ulnar and peroneal nerves, most commonly), a third stimulation site may be used. To obtain a motor nerve conduction velocity, the latency (the time it takes from stimulus to response) obtained from the distal (wrist or ankle) stimuli is subtracted from the latency of the proximal stimulation. The latency difference is divided into the distance between the two stimulating sites to obtain the nerve conduction velocity.

The sensory nerve conduction studies may only require one stimulation site, although some laboratories use two sites. Some laboratories stimulate the nerves as they do in the motor studies, but

on the hand, they place ring electrodes on the finger (antidromic studies). Other laboratories will stimulate with the rings and record with pads over the wrist (orthodromic studies). The sensory potentials are of very low amplitude, about 1/1000 of the motor responses, and they require the averaging of at least five responses to identify the response above both the baseline and random activity. This will require multiple stimuli, usually less than 10, but sometimes many more. The level of intensity is typically not as great as for motor studies, so the discomfort level is a bit less.

Patients tolerate the sensory nerve conduction studies best if they relax their limbs and breathe comfortably. Usually the technician begins with very low stimulus intensity and alerts the patient when the stimulus will occur. Remember, the study does not endanger the patient and any discomfort lasts less than a second. The nerve conduction portion of the study takes 30 minutes to one hour, depending on how many nerves are tested. Each motor or sensory nerve takes about 10 minutes—most of that time is spent placing the electrodes, measuring distances and marking the responses. The actual stimulation time is only a fraction of the 10 minutes. When the responses are outside of normal ranges, however, the study can take longer.

The second part of the electrodiagnostic evaluation is the needle EMG. Most patients fear this part of the examination the most, but in reality, most patients experience less discomfort during this portion of the evaluation when compared to the conduction studies. People who have needle phobias may have difficulties with the study, and in some circumstances the patient and physician may decide that the information gained from the test may not be enough to warrant the psychological trauma. Needle EMG may not be needed in all instances, but in some circumstances, it may be the only way to determine whether the disorder is due to neuropathy or muscle disease, and to determine which muscles are involved.

The needle EMG is a very safe study. Disposable needles are used, so there is no risk of the patient contracting an infectious illness, such as HIV or hepatitis. The physician may wear gloves to avoid the risk of exposure to a patient's contagious illness in the event of an accidental needle stick. The needles are very thin and sharp (they bear more resemblance to a wire than a needle) and the discomfort is usually less than one would experience when one is having blood drawn. Patients on blood thinners should not have the needle inserted too deeply or in muscles that are deep beneath the skin surface, but there is usually no problem when superficial muscles are studied. Whether to do the study on people on blood thinners is determined after discussion between the physician and patient.

The study is done by inserting the needle in the muscle and observing the electrical potentials when the muscle is at rest, with minimal activation and with maximal effort. The physician observes the potentials as they move across the screen and also listens to the sounds that the potentials make. The needle is usually in the muscle for fewer than three minutes. It is usually not painful to have the needle in the muscle, although certain regions of the muscle are pain sensitive. The physician can usually identify these regions and move the needle. There is usually very little bleeding, although occasionally a small black and blue area can develop. It is typically very easy to stop any bleeding that may occur, even in patients on blood thinners or on aspirin.

Electrodiagnosis of children

Children do not encounter any increased risks during electrodiagnostic evaluations. Studies can be performed on newborns and children of all ages. Some children are scared of the procedure, but typically, they can be calmed down and they will allow at least one motor nerve conduction study. In infants, the only way that the study can be accomplished is by restraining the child. This issue needs to be discussed with the parents in advance so that they

understand how the evaluation is being performed. If older children cannot be calmed, restraints may also be considered, but whether to proceed with the study must be discussed. It is not uncommon for children to cry during the study. Parents need to be prepared for such an occurrence and understand that it is usually best to allow the study to be completed as quickly as possible. Some physicians prefer that the parents be out of the exam room during the testing, because frequently it is easier to calm the child when the parents are not present. All of these issues should be carefully and sensitively discussed prior to performing the studies.

Information obtained from electrodiagnostic evaluations

The most important information obtained from conduction studies is the motor and sensory conduction velocities, the amplitude of the responses and the shape of the responses. The physician is interested in whether all the nerves respond in a similar manner or if there is evidence of multifocal involvement. The interpretation of the results is based on the comparison of the speed of conduction to the amplitude of the response.

The needle EMG study can determine if the muscle has lost its innervation (the ability of the nerves to stimulate the muscle to action) and if there is a primary disorder of the muscle. Motor units (a group of muscle fibers innervated by one motor nerve fiber and motor neuron) are usually very small in muscle diseases and very large in chronic neuropathies. The number of motor units activated in muscle diseases is usually normal, while the number of motor units is reduced in nerve disorders. This means that in muscle diseases there are normal numbers of motor units, but these units are small and weak and the patient needs to recruit more units than normal to obtain a strong muscle contraction. In neuropathic disorders there is a loss of motor units, but in chronic diseases the remaining motor

units take up muscle fibers that have lost their innervation. This makes each unit larger than normal.

Electrodiagnosis in CMT

The first thing that the clinician needs to know is whether someone suspected of having CMT truly has a neuropathy. Occasionally, someone with a muscle disorder can present with very similar clinical problems. Any conduction velocity or amplitude abnormality suggests a neuropathy.

The next issue is whether the neuropathy is purely motor, purely sensory or both motor and sensory. Most cases of CMT involve both motor and sensory nerves, but pure motor and pure sensory disorders are recognized and the genetic mutations causing them are frequently different from those with a mixed picture. Differentiating between purely motor, purely sensory or both motor and sensory allows the clinician to focus on the genetic problems that are most likely to be involved, rather than ordering diagnostic genetic tests for all genes that have been implicated in CMT.

One of the most important diagnostic goals related to CMT is to determine whether a family has CMT1 or CMT2. CMT1 includes disorders in which the genetic mutation primarily affects myelin and its cell, the Schwann cell. Myelin acts, in part, as an insulator to the nerve fiber (axon) and allows the nerve to conduct electrical potentials at very fast rates. In the case of CMT2 disorders, the genetic mutations affect the nerve fiber—the axon.

CMT1 is defined by very slow nerve conduction velocities. For example, normal nerves in the arm conduct at more than 50 meters/second (m/sec) (Figure 2), but the nerves of patients with CMT1 conduct at less than 38 m/sec, and most commonly at 20-30 m/sec (Figure 3). Some severe forms of CMT1 will result in conduction rates as slow as 5 m/sec. CMT2, however, has much

faster velocities, usually more than 40 m/sec.

Velocities between 30 and 40 m/sec are called CMT intermediate. Most of the families in this group have disorders caused by mutations to genes associated with myelin production, but the mutations have less of an effect on conduction speed. The most common CMT intermediate forms with adult onset (CMT1X, caused by mutations of the *CX32* gene and CMT1B, caused by mutations of the *MPZ* gene), frequently have conduction velocities in the intermediate range. Interestingly, childhood onset CMT1B (with different *MPZ* mutations) have very slow velocities—under 10 m/sec. Thus, in CMT intermediate disorders in which the *MPZ* gene is associated, both the clinical picture and the nerve physiology can be dramatically different, depending on the type of gene mutation.

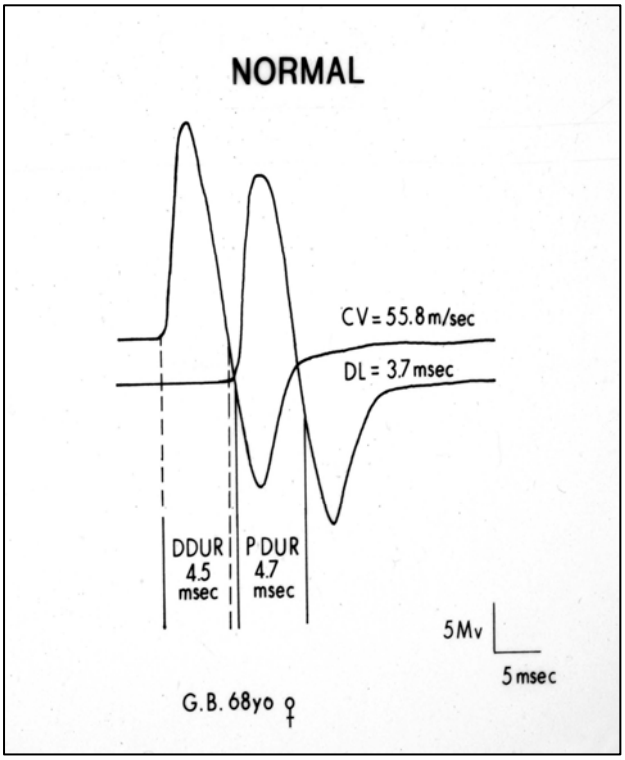

Figure. 2. Normal Nerve Conduction Study.

- CV = Conduction Velocity
- DL= Distal Latency
- DDUR = Distal Duration
- PDUR = Proximal Duration

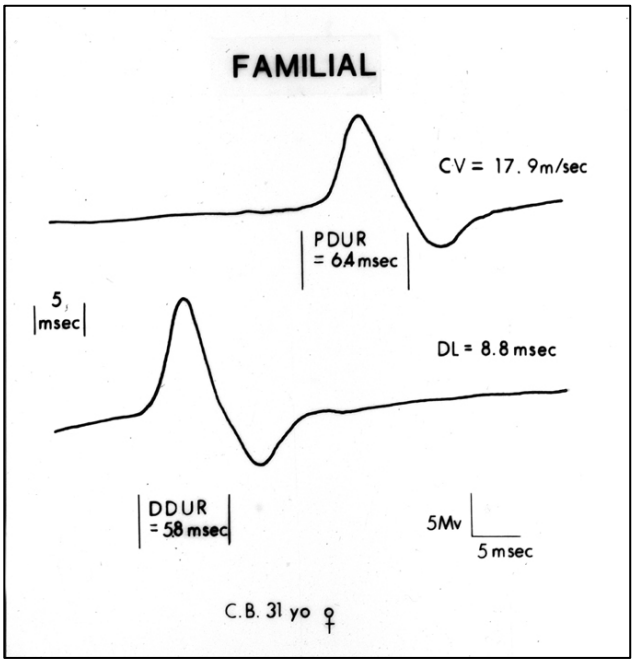

Figure 3. Familial Study of CMT1A Patient.

Other findings from electrodiagnostic studies shed light on the diagnosis of different forms of CMT. Different patterns of conduction slowing point to different disorders. For instance, the most common form of CMT, CMT1A (caused by a duplication mutation of the *PMP-22* gene), has conduction velocities of around 20-25 m/sec in every nerve tested; this is called uniform conduction slowing. Conversely, CMT1X has non-uniform slowing.

In many of forms of CMT, electrodiagnosis can be used to determine if an asymptomatic family member has the genetic disorder. This is particularly useful in the diagnosis of CMT1A, in which one motor nerve conduction study can usually determine if a child or adult has the disorder.

Electrodiagnosis points out that the degree of disability usually does not correlate to how slow the nerves conduct, but instead, correlates with how many nerve fibers are functioning. The amplitude of the responses is one of the best indicators of the amount of nerve fiber loss. The lower the amplitude, the fewer number of functioning nerve fibers. Newer techniques, such as Motor Unit Number Estimation, are being used to determine the number of functioning nerve fibers.

Summary

Electrodiagnostic studies are extremely important in the evaluation of patients with suspected CMT. The studies can determine if the patient has a neuropathy, whether the neuropathy is pure motor, pure sensory or both motor and sensory, and can determine if the genetic disorder primarily affects the axon or the myelin. In addition, the studies can determine the extent of axonal loss and the distribution of the loss.

While the studies are remarkably safe, they do require procedures that may be uncomfortable. With knowledge, discussion and preparation, the degree of discomfort can be minimalized and

patients of all ages can benefit from the important information these studies yield.

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The Pathology of CMT

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The structure of myelinated axons

In the mature peripheral nervous system, Schwann cells form myelin sheaths around most axons that are one micron in diameter or larger. All axons that innervate skeletal muscle (motor axons), as well as a subset of sensory axons, are myelinated. As shown in Figures 1A and 1B, the bulk of the myelin sheath is formed by layer upon layer of cell membranes, called compact myelin. The cell membrane itself is highly specialized, containing a higher proportion of lipids (fats) than typical cell membranes, as well as specialized lipids (galactocerebroside and sulfatide) and proteins (myelin protein-zero [P0], peripheral myelin protein 22 kDa [PMP22], myelin basic protein [MBP]) that are not found in most cell membranes. Because P0 is the molecular “glue” that holds together the cell membranes, it is not surprising that mutations in the *MPZ* gene, the gene that encodes the protein P0, cause demyelination. The function of PMP22 is unknown, but genetic evidence strongly suggests that precisely the right amount is required for the stability of the myelin sheath—halving the amount of PMP22 causes hereditary neuropathy with liability to pressure palsies (HNPP) and increasing the amount of PMP22 by one-half causes CMT1A.

A different set of molecular specializations characterizes other parts of the myelin sheath—so-called “non-compact myelin” (Figure 2). Non-compact myelin is found in the paranodes (at the lateral edges of the myelin sheath) and incisures (funnel shaped disruptions of

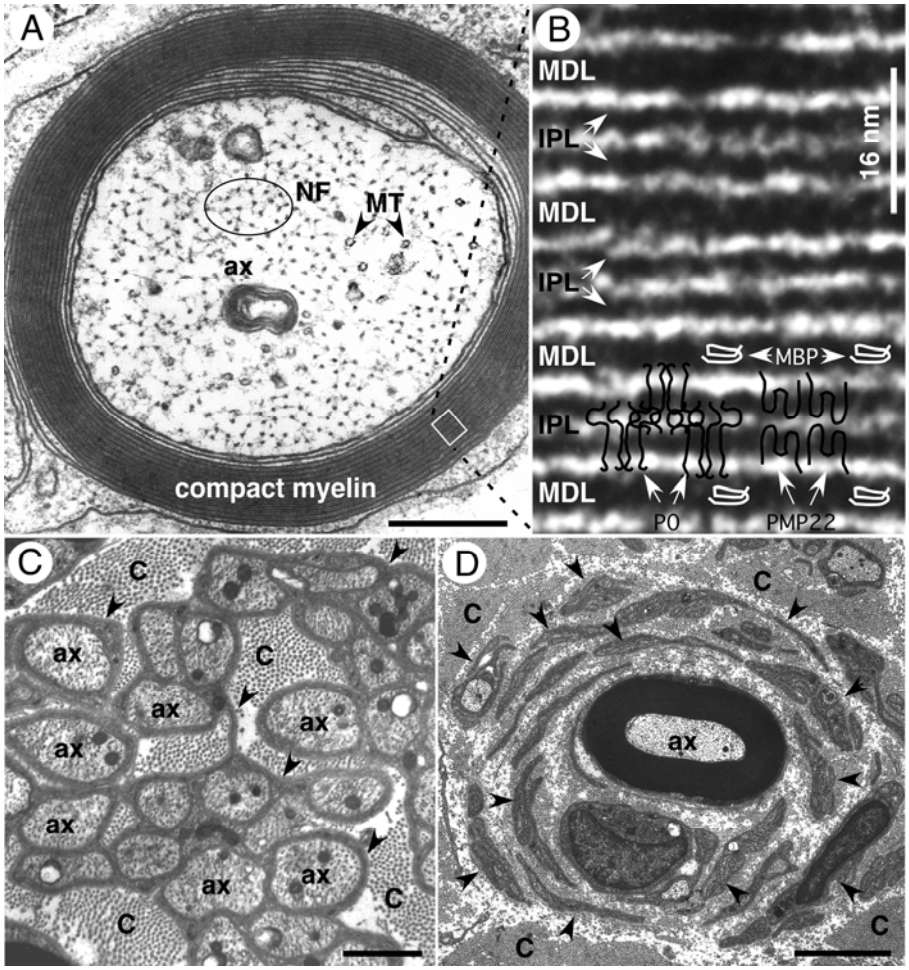

Figure 1. Ultrastructural features of axons (images made with an electron microscope).

A: **Myelinated axon.** The axon (ax) mostly consists of neurofilaments (NF), a group of which is enclosed by the oval, and microtubules (MT), two of which are marked by arrowheads. The axon is surrounded by compact myelin, a portion of which (rectangle) is enlarged in Panel B. From a mouse sciatic nerve. Scale bar: 0.5 microns.

B: **Compact myelin.** This is composed of a single, major dense line (MDL) that alternates with a doublet of interperiod lines (IPL; arrows). The disposition of P0 (tetramers), PMP22 (dimers), and MBP (monomers) in the compact myelin is indicated. The distance between the major dense lines is about 16 nanometers.

C: **Unmyelinated axons.** These unmyelinated axons (ax) are ensheathed by the relatively darker processes (arrowheads) of Schwann cells. C = collagen fibers. From a mouse sciatic nerve. Scale bar: 0.5 microns.

D: **Onion bulb.** This was one of many found in a sural nerve biopsy from a 59-year-old who has CMT1. A myelinated axon (ax) is surrounded by crescents of Schwann cell processes (arrowheads); considered to be reminiscent of an onion cut in cross section. C = collagen fibers. Scale bar: 5 microns.

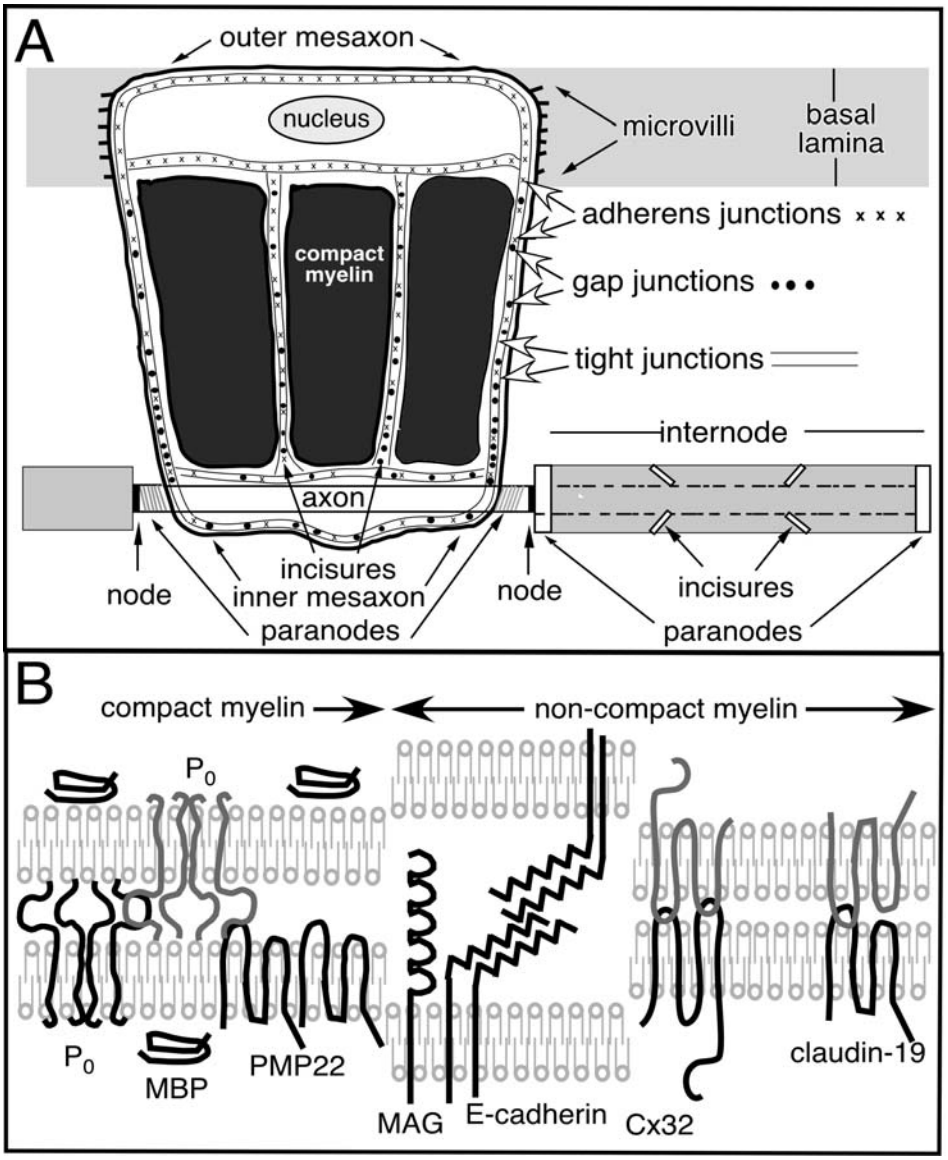

Figure 2. Junctional specializations in the peripheral nervous system myelin sheath.

A: A myelinating Schwann cell has been "unrolled" to reveal its trapezoidal shape; the two lateral edges define the paranodes. Non-compact myelin is found in the paranodal region and in incisures. Tight junctions are depicted as two continuous lines; these form a circumferential belt and are also found in incisures. Gap junctions are depicted as ovals; these are found between the rows of tight junctions. "X" indicates adherens junctions.

B: Schematic representation of the proteins of compact and non-compact myelin. Compact myelin contains P0, PMP22, and MBP; non-compact myelin contains E-cadherin, myelin-associated glycoprotein (MAG), CX32 and claudin-19.

compact myelin). Non-compact myelin contains the molecules that form specialized junctions (claudins form tight junctions, connexins form gap junctions and cadherins form adherens junctions) between the cell membranes of non-compact myelin. Gap junctions form a pathway for the diffusion of small molecules and ions directly across the myelin sheath and are formed by two apposed hemi-channels, which in turn, are formed by six connexin molecules. Mutations of *GJB1* (the gene that encodes the gap junction protein connexin32) cause the X-linked form of CMT1, presumably because the mutant proteins do not form functional gap junctions in the myelin sheath.

Demyelinating neuropathies

Myelin sheaths are formed in an orderly sequence during development. After ensheathing an axonal segment, each myelinating Schwann cell forms a sheet of cell membrane that repeatedly spirals around and around the axon, forming the multiple layers that constitute the myelin sheath. The length of the nascent myelin sheath is about 50 microns. Individual axons appear to be myelinated synchronously along their length and the subsequent growth in that region of the body results in the elongation of myelin sheath. The axons destined to become the largest are the first to be myelinated; the smallest myelinated axons are myelinated last. The result of these developmental processes is that the myelin sheaths (called internodes) of individual myelinated axons have remarkably similar lengths and that the internodal lengths are linearly related to their axonal diameter. In addition, the myelin sheath and axon itself constitute about 40 percent and 60 percent, respectively, of the total diameter of the myelinated axon, regardless of the axonal diameter. If a myelin sheath breaks down, for whatever reason, the demyelinated internode is typically remyelinated. Because there is little “turnover” of myelin sheaths in normal nerves, abnormally thin myelin sheaths and abnormally short internodes are important pathological findings that are used to diagnose demyelinating neuropathies (Figure 3).

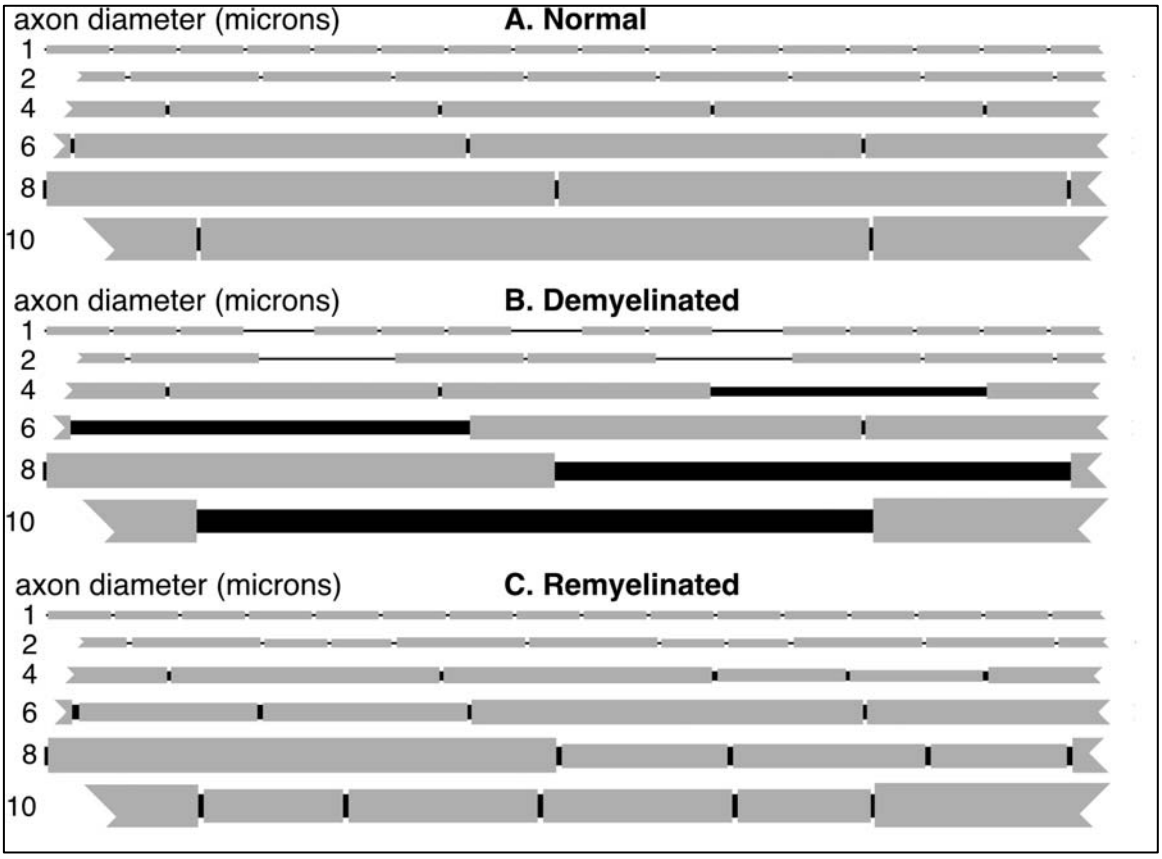

Figure 3. Schematic summary of demyelination and remyelination.

A. Six myelinated axons from a normal nerve are depicted individually; the axon is drawn as a solid black line that is surrounded by a series of myelin sheaths/internodes (gray rectangles) that are separated at nodes of Ranvier. Note that the largest axons have the longest and thickest myelin sheaths, which are uniform along the length of the axon. The internodal lengths shown here are not shown to scale—they should be much longer, roughly 100 times the axonal diameter. Thus, an axon 1 micron in diameter has 100 micron long internodes; an axon 10 microns in diameter has 1000 micron long internodes.

B. One or more internodes per myelinated axon have been removed (depicting acute demyelination), revealing the underlying axon. Even acutely demyelinated segments would be typically ensheathed by Schwann cells that have not yet made myelin sheaths; "naked axons" are uncommon in demyelinating neuropathies.

C. Demyelinated internodes after remyelination. Note that the remyelinated internodes are shorter and thinner than the original internode they replaced.

Most of the autosomal dominantly inherited (CMT1A – CMT1D) and autosomal recessively inherited (CMT4B – CMT4F) demyelinating neuropathies show evidence of repeated demyelination and remyelination. The more severe forms of CMT, historically known as Dejerine-Sottas Neuropathy (DSN) and Congenital Hypomyelinating Neuropathy, have the most pronounced demyelinating/remyelinating pathologies. In these neuropathies, the "left over" Schwann cells (generated by proliferation during demyelination) that surround the remyelinated internode form onion bulbs (Figures 1D, 4C and 4D). By comparison, demyelination and remyelination are not nearly as pronounced in CMT1X and CMT4A, and it is possible that CMT4A is not truly a demyelinating neuropathy. In addition to the demyelinating forms of CMT, demyelination/remyelination is a feature of some autosomal dominant syndromes (such as those caused by *SOX10* mutations) and autosomal recessive syndromes (such as metachromatic leukodystrophy and globoid cell leukodystrophy [Krabbe disease]).

In addition to the presence of demyelination and remyelination, the proportion of demyelinated/remyelinated axons correlates with the severity of the neuropathy (Figure 4). Fewer myelinated fibers, thinner myelin sheaths and slower conduction velocities are associated with more severe neuropathies. Demyelinated axons appear to atrophy as well (Figure 4); this is associated with the dephosphorylation (the removal of phosphate groups) of neurofilaments and the tighter packing of the neurofilaments within axons. Some demyelinating neuropathies have particular pathological findings—tomaculi (thickening of the myelin sheaths) in HNPP (Figure 4), uncompacted myelin in some cases of CMT1B, "focally folded" myelin sheaths in CMT4B1 and CMT4B2, and the accumulation in Schwann cells of undegraded glycolipids in metachromatic and globoid cell leukodystrophies. Even in hereditary demyelinating neuropathies, progressive axonal loss—not demyelination, per se—is the cellular basis for the clinical disability. In CMT1A, for example, longitudinal studies show that conduction

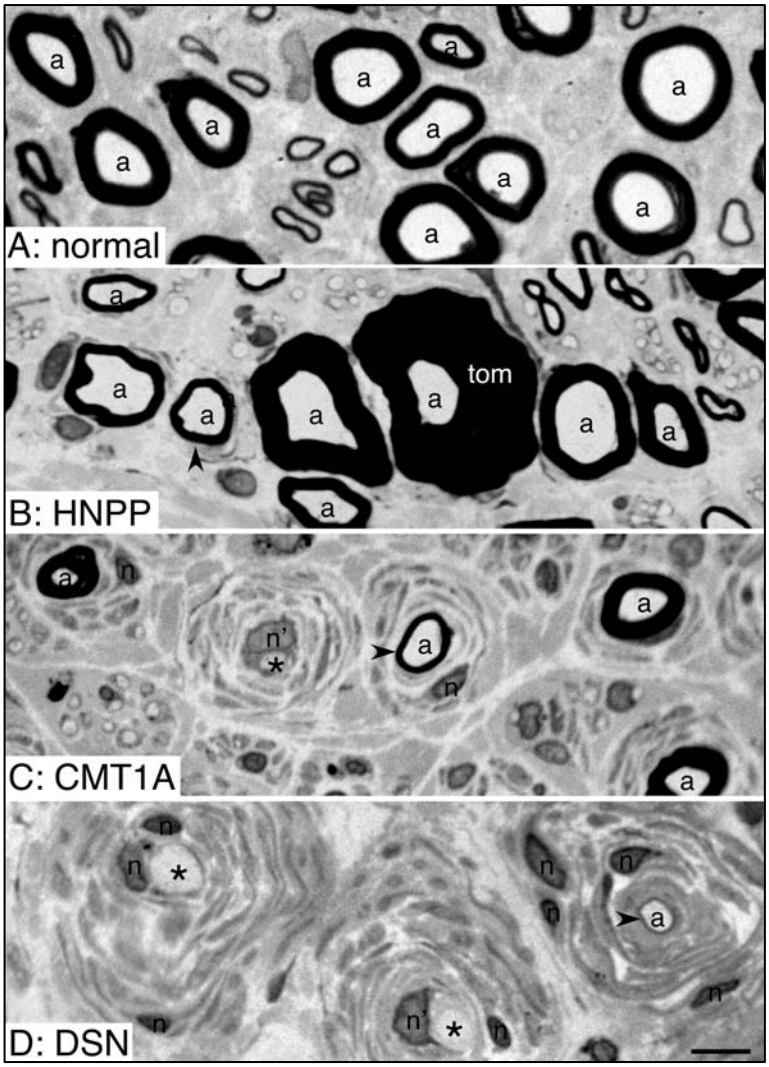

Figure 4. Pathological features of HNPP, CMT1 and DSN.

These are photomicrographs of semi-thin sections of sural nerve biopsies from:

A. A 27-year-old with normal findings

B. A 32-year-old with HNPP

C. A 46-year-old with CMT1A. Note the tomaculum (tom)

D. A 16-year-old with autosomal dominantly inherited DSN

Myelinated axons (a); demyelinated axons (*) and their associated Schwann cell nuclei (n'); remyelinated axons (arrowheads).

In C and D, note the supernumerary Schwann cell processes and their nuclei (n) that form onion bulbs around demyelinated and remyelinated axons.

Scale bar: 10 microns.

velocity does not change after a few years of age, whereas axonal loss is progressive. Thus, preventing axonal loss is a plausible (and hopefully feasible) goal for treating CMT.

Axonal neuropathies

The selective vulnerability of peripheral nervous system neurons that leads to neuropathy may be the axons themselves; the length of axons makes them the longest cells in the body. Axons have a prominent cytoskeleton composed of intermediate filaments and microtubules (Figure 1A). Neurofilaments are the main neuronal intermediate filament and comprise three subunits: heavy, medium and light. Dominant mutations in *NEFL*, the gene encoding the light subunit, cause an inherited axonal neuropathy (CMT2E). Because axonal protein synthesis is scant, proteins must be transported down the axon after they are synthesized in the cell body. Axonal transport is mediated by microtubule-activated ATPases, known as kinesins, molecular motors that use microtubules as tracks; different kinesin transport different organelles. Axons have plentiful mitochondria, which are presumably the main source of axonal ATP.

Sural nerve biopsies from CMT2 patients show reduced numbers of large myelinated axons, clusters of regenerated axons, and few onion bulb-like structures. (The sural nerve is located on the lateral surface of the leg; it begins behind the knee and reaches to the lateral surface of the foot.)

Axonal loss is slow and progressive, so that actively degenerating axons are rarely detected in nerve biopsies. Myelinated axons are transformed into cords of Schwann cells not associated with any axons (known as bands of Büngner), and even these disappear with time, leaving the nerve with fewer cells and more collagen.

Many axons are not myelinated. These are smaller than myelinated axons and multiple axons are typically ensheathed by a single, non-

myelinating Schwann cell (Figure 1C). Many sensory neurons (including those that convey pain information) and autonomic neurons (which innervate glands and smooth muscle) have unmyelinated axons. The term “small fiber neuropathy” denotes a neuropathy in which unmyelinated axons are selectively involved. With a few exceptions (such as Fabry disease), these neuropathies are acquired, not hereditary. In some kinds of hereditary sensory (and autonomic) neuropathies, there may be prominent loss of unmyelinated axons owing to the congenital loss of their associated cell bodies.

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Genetics of Charcot-Marie-Tooth Disorder

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Charcot-Marie-Tooth disease (CMT). one of the most common of all inherited diseases, is a classic example of genetic heterogeneity, which is a phenomenon of mutations that occur in various genes, usually on separate chromosomes, and independently produces an identical phenotype, or clinical appearance. CMT is caused by various genes, but they can be inherited in different patterns. Therefore, in order to accurately provide information to a CMT family, one must know the type of CMT (CMT1 or CMT2) and the inheritance pattern of CMT within that family. At present (2006), more than 35 separate gene mutations can cause the CMT phenotypes following autosomal dominant, X-linked inheritance, or autosomal recessive patterns (CMT4) (Inherited Peripheral Neuropathies Mutation Database). While CMT4 has a similar clinical presentation to that of more common autosomal dominant and X-linked forms, its usually earlier onset and greater severity often differentiate it from these

types. CMT genes that fall into the traditional classification are discussed here (see Table 1). However, there are a number of genes that are not described in detail that can cause rare or unusual forms of CMT. The discovery of new CMT genes has progressed, and it is not unrealistic to expect that in the future we will know of about 50 genes—all associated with the CMT phenotype. This situation presents challenges of its own for genetic testing and for the field of CMT research.

Demyelinating autosomal dominant CMT type 1

At least four different gene defects are known that cause CMT type 1 (demyelinating CMT with slow nerve conduction velocities (NCV)). The gene defect for the vast majority of autosomal dominant CMT type 1 families is located on chromosome 17p11.2 (CMT1A) (Boerkoel, 2002; Choi, 2004). Within this classification of CMT1A, two specific mutation mechanisms exist: the majority of patients (about 70 percent) have a large area of 1.5 million base pairs of the chromosome duplicated. The other CMT1A families do not have the duplication; instead they have an abnormal base pair substitution in the gene that produces the myelin protein PMP22. PMP22 is known to lie within the chromosomal duplication as well. Interestingly, a loss or deletion of the same chromosomal region leads to a phenotype called hereditary neuropathy with liability to pressure palsy (HNPP). PMP22 mutations represent the vast majority of classic CMT1 cases with reduced NCVs. However, some mutations have been shown to be associated with a primarily axonal phenotype that mimics CMT2 (Thomas, 1999).

CMT1B is caused by mutations in the gene myelin protein zero (MPZ). Mutations in MPZ are not a rare cause of CMT1 and should be included in all screening efforts. MPZ is a myelin protein, thus acting in the dense myelin sheaths that surround the fast transmitting axons in peripheral nerves. Like PMP22, some MPZ mutations can cause a phenotype that resembles CMT2. In particular, some MPZ

Table 1: Genetically defined CMT subtypes and their clinical characteristics.

CMT type	Gene	NCV	Clinical characteristics
CMT1A	PMP22	Mostly decreased/ some preserved	
CMT1B	MPZ	Mostly decreased/ some preserved	Adie pupil
CMT1C	SIMPLE	Decreased and preserved	
CMT1D	EGR2	Decreased	Dejerine-Sottas syndrome
CMTX	CX32/GJB1	Decreased	White matter changes
CMT2A	MFN2	Preserved	Classic CMT2, some optic atrophy
CMT2B	RAB7	Preserved	Predominant sensory involvement, lower leg ulcers
CMT2D	GARS	Preserved	Predominant hand involvement
CMT2E	NEFL	Preserved/ moderately decreased	
CMT2F	HSP27	Preserved	
CMT2L	HSP22	Preserved	
DI-CMTB	DNM2	Preserved/ moderately decreased	Neutropenia
DI-CMTC	YARS	Preserved/ moderately decreased	
CMT4A	GDAP1	Preserved and decreased	
CMT4B1	MTMR2	Decreased	
CMT4B2	SBF2	Decreased	Glaucoma
CMT4C	KIAA1985	Decreased	Scoliosis
CMT4F	Periaxin	Decreased	Dejerine-Sottas
CMT2B1	Lamin A/C	Preserved	

mutations might affect the way a person's pupil works, creating an eye condition known as Adie pupil. The reason that certain mutations have seemingly different effects on the peripheral nerve is still not understood (Shy, 2004).

The underlying gene for CMT1C has recently been identified and is named LITAF/SIMPLE. Mutations in SIMPLE account for up to 8 percent of all CMT1 cases. Its molecular role has been linked to protein degradation (ubiquitination). Physicians should be aware that a small number of axonal or CMT2 phenotypes can be caused by certain SIMPLE mutations (Saifi, et al., 2006; Street, et al., 2003).

CMT1D is a rare CMT form caused by mutations in the gene EGR2. The phenotype is usually very severe. In addition, a so-called congenital hypomyelination syndrome can be caused by EGR2 mutations. EGR2 protein represents a transcription factor that initiates the development of the dense myelin sheaths that surround nerve fibers in the peripheral nerve (Warner, et al., 1998).

Axonal autosomal dominant CMT type 2

Reported estimates indicate that CMT2 comprises approximately one-third of all instances of the CMT phenotype (Harding & Thomas, 1980). But surely this is an underestimate, insofar as many cases seen by physicians do not take the family history into account and the patients are classified among those with nonspecific axonal neuropathies. Most families with CMT2 have genetic characteristics that follow an autosomal dominant inheritance pattern. The age at disease onset can vary significantly from childhood up to the sixties—even in the same family. However, all individuals who carry the causative mutation will normally develop disease symptoms. Furthermore, since the NCVs are essentially normal in CMT2, the diagnosis is for the most part clinical. For those reasons, the research to identify CMT2 genes has lagged behind that for the CMT1 genes. During the past five years, however, several major

CMT2 genes have been identified. A number of studies screened for the frequency of mutations in certain CMT2 genes, and researchers tried to identify specific clinical subphenotypes. For some of the CMT2 genes, it appears possible to predict the affected gene through careful clinical assessment, but for the majority of CMT2 cases a large number of genes have to be screened for mutations.

CMT2A was the first CMT2 locus described, and the underlying gene has been identified as *mitofusin 2* (MFN2). It turns out that MFN2 mutations are by far the most common cause for axonal CMT. Estimates range from 8 percent to 20 percent in different studies and populations (Zuchner, et al., 2004; Kijima, et al., 2005). The mutations were usually point mutations that cluster in the so-called GTPase domain of the translated protein. The MFN2 protein plays an important role in the fusion-fission balance and the transport of mitochondria. Mitochondria are the powerhouses of cells and since nerve cells have a high energy demand, they are more susceptible to mitochondrial malfunction. Up until now, all studies have shown a classic CMT2 neuropathy in the affected families. Some rare cases also show involvement of the central nervous system. For example, a subgroup of CMT2A patients with an early onset of CMT also develops a decrease in visual acuity (optic atrophy). This subtype has also been designated HMSN VI (Zuchner, et al., 2006).

Research on CMT2B has shown that it is caused by mutations in the Ras-associated protein RAB7 (RAB7). CMT2B is a rare cause for CMT2. Unlike most cases of CMT2, the sensory system in CMT2B is affected to a greater extent than the motor system. This causes the patient to develop leg and foot ulcers that can sometimes lead to infection and the subsequent necessity to amputate (Verhoeven, et al., 2003).

CMT2D is caused by mutations in glycyl-tRNA synthetase (GARS). The clinical phenotype is often associated with the initial presentation of CMT in the hands rather than in the lower extremities, which is

more usual. Thus, a careful clinical examination could direct the genetic testing of a small subgroup of patients toward GARS. CMT2D is a rare cause for axonal CMT (Antonellis, et al., 2003).

CMT2E was the first CMT2 form in which the causal gene, neurofilament light (NEFL), was identified. NEFL mutations can be found in about 2 percent of all CMT2 cases (Mersiyanova, et al., 2000). The associated NCV includes CMT2 and patients with moderately slowed NCVs. These latter cases are sometimes classified as intermediate CMT. NEFL is an important structural protein that provides a component of the cytoskeleton. The cytoskeleton is a meshwork of fibers that stabilizes the shape of cells and also serves as a network of rails for intracellular transport of cellular organelles.

CMT2F is caused by mutations in the gene HSP27. Interestingly, various mutations in the same gene cause a motor neuron disease with a separate clinical phenotype. All documented CMT patients have had a classic CMT2 phenotype. CMT2F mutations are also rare (Ismailov, et al., 2001).

Finally, CMT2L is a rare cause for CMT caused by mutations in the gene HSP22. HSP22 is related in cellular function to the CMT2F gene HSP27. Both genes ensure and protect the correct folding of proteins. Up until now, all documented patients are of Chinese ethnicity (Tang, et al., 2005).

X-linked CMT

Almost all X-linked CMT cases have a mild reduction of NCVs termed intermediate slowing; since the NCVs are borderline for demyelination classification, sometimes cases may resemble CMT1 and other times look more like CMT2. However the Cx32 protein is expressed in the myelin, not the axon. Often, it can be difficult to tell if a family has the X-linked form of CMT1 or autosomal dominant

inheritance. However, if an affected male has an affected son, the disease cannot be CMTX (the reason is that in order to have a boy child, the father has to provide the Y-chromosome instead of the X-linked disease to his male offspring). All the female offspring of an affected male with X-linked CMT will have the CMTX mutation although they usually (but not always) will have, at most, mild symptoms. One-half of an affected woman's offspring (regardless of the sex of the child) will inherit the mutated gene.

The gene for the most common form of X-linked CMT is Gap Junction Beta 1 *(GJB1)* that encodes protein connexin 32 (Cx32), also known as *gap junction protein beta 1* (GJB1). It is a relatively frequent cause for CMT. Because the gene product is part of the myelin sheath that surrounds the larger axons in peripheral nerves, it can be classified as a CMT1 gene. The molecular functions of Cx32 have been studied extensively; however, a specific target for drug interaction has not evolved (Fischbeck, et al., 1999). Interestingly, Cx32 mutations are in some cases associated with fluctuating changes of the white matter of the brain, without causing neurologic symptoms (Hanemann, et al., 2003).

Strong evidence exists for additional X-linked CMT genes, but those have not yet been identified.

Recessive CMT type 4

This form has been described in the medical literature both in Europe and in North America during the past 50 years or more. However, because of its inheritance pattern, it is much less common in these geographic regions than it is in North Africa and South America. Usually both parents of an affected child are clinically normal carriers of the disease. In the period of time since a number of recessive CMT genes have been identified, mutations have been found, mostly in small CMT families with only one or two affected individuals.

CMT4A is the most common form of recessive CMT; it is caused by mutations in the gene ganglioside-induced differentiation-associated protein 1 (GDAP1) (Baxter, et al., 2002; Cuesta, et al., 2002). So far about 25 different mutations have been identified. Interestingly, GDAP1 mutations cause both demyelinating and axonal phenotypes. The axonal forms are often associated with a hoarse voice due to paresis of the vocal cord. Affected patients have early CMT symptoms and the condition usually deteriorates, so that most patients are wheelchair-bound by the time they reach the age of 10 years. There has been recent evidence that GDAP1 can also be transmitted in an autosomal dominant pattern, but this appears to be the exception rather than the rule.

CMT4B is classified into two subtypes: CMT4B1 and CMT4B2. The first one is caused by mutations in MTMR2 and the latter by mutations in SBF2, also known as MTMR13 (Bolino, et al., 2000; Senderek, et al., 2003). The CMT in CMT4B2 is sometimes associated with the development of early-onset open-angle glaucoma (Hirano, et al., 2004). Both CMT4B forms have characteristic pathologic myelin changes in biopsies of the sural nerve.

CMT4C is caused by mutations in the gene KIAA1985. Most of the reported families were from North Africa. CMT4C is a demyelinating form of CMT. A considerable number of CMT4C patients had scoliosis. Biopsies of the sural nerve showed prominent onion- bulb formation of basal lamina from Schwann cells (Senderek, et al., 2003).

Summary

The CMT phenotype continues to be not only one of the most commonly inherited diseases known in mankind, but certainly one of the most genetically heterogenous. The limited sensitivity of past clinical nerve conduction and electromyographic examinations in defining these diseases is now being replaced by definitive genetic

classifications and testable genes. Therefore, it is no longer sufficient to refer to these patients as having CMT disease, which implies merely a single entity. Rather, these disorders would be better termed the CMT phenotype, consisting of an increasingly complex set of different genetic diseases. The continuing elucidation of this phenotype will not only provide insight into these disorders but will also open avenues of study to the mechanisms of the normal peripheral nerve.

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Charcot-Marie-Tooth Disorders in Children

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Classification and prevalence of Charcot-Marie-Tooth disease (CMT)

CMT, also known as hereditary motor and sensory neuropathy (HMSN), encompasses a group of clinically and genetically heterogeneous inherited polyneuropathies. Initially they were simply classified in accordance with their clinical presentation, mode of transmission (autosomal dominant, autosomal recessive, or X-linked), and electrophysiological pattern or nerve biopsy features (either demyelinating or axonal).[1] Starting from these data, seven main disease categories were distinguished, though most cases could be categorized as HMSN I (demyelinating pattern with autosomal dominant or X-linked transmission), HMSN II (axonal pattern with autosomal dominant or autosomal recessive transmission) and HMSN III (severe demyelinating/hypomyelinating neuropathy with autosomal recessive transmission or Dejerine-Sottas disease).

In the last decade, the CMT classification has been in a state of constant flux, reflecting the rapid advances in the description of causative genes.[2] Classification of the disease is at present based upon clinical and genetic data comprising about 40 loci.[3] To retain the memory of such items seems to be an almost impossible task. On that score, it is timely to recall the quotation by Anita Harding[4]

commenting on the seven forms of HMSN in Dyck's classification: "I do not find this very useful, having difficulties in remembering any classification of disease with numbers greater than three". Because of this and from the practicing clinicians' point of view, diagnostic strategy in CMT should still begin with a detailed clinical history and examination of the affected individual and relatives, followed by electrophysiological study; nerve biopsy is now reserved for some familial forms, and sporadic or doubtful cases. At this stage, it is usually possible to reach a presumptive diagnosis of HMSN I (CMT1), HMSN II (CMT2) or HMSN III (including Dejerine-Sottas syndrome, CMT4 and autosomal recessive CMT2).

Global prevalence of CMT is reported to be 28 cases per 100, 000 inhabitants,[5] whereas in children aged 2-15 years the range may be around 19/100,000.[6] The most common genotype is CMT1A, characterized by autosomal dominant transmission and a large DNA duplication on the short arm of chromosome 17 containing the *PMP22* gene. In this chapter, we will focus primarily on studies performed in CMT1A children.

Clinical presentation

The clinical course is non-progressive in adult patients, though a significant age-dependent increase of either mean weakness score or neuropathic deficit has been reported in cross-sectional studies; furthermore functional disability increases with disease duration. In a transversal study, Harding and Thomas[7] established that symptoms are present during the first decade of life in more than 60% of HMSN I patients. We addressed this question by performing a longitudinal study over two decades in 12 secondary CMT1A children, aged between 1 month and 5 years (mean age, 2 years) at first initial examination, and final ages (in 2002) between 6 and 23 years (mean age, 13 years).[8,9,10] Initially, only 2 (17%) patients had developed symptoms, whereas at the end of the study 5 (42%) patients were symptomatic. Symptomatic children were at most only slightly disabled, the cardinal symptoms being some difficulty in running or

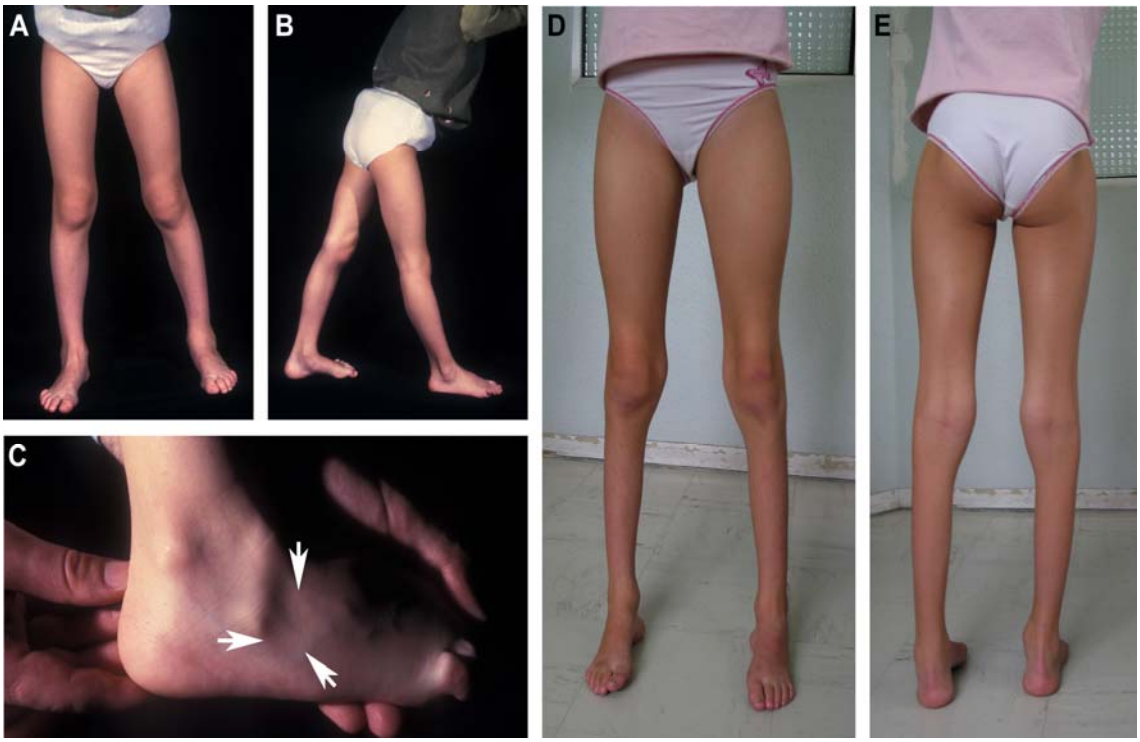

Figure 1. Pictures of a girl suffering from CMT4A due to point missense mutation in the *GDAP1* gene. Her parents reported a delay in motor milestones and clumsy walking. At age 6, note the development of peroneal (fibular) muscular atrophy, toe clawing and bilateral pes cavus (high arches) (**A** and **B**) and marked atrophy of extensor digitorum brevis (EDB) muscle (**C**, arrows). Five years later, note severe leg amyotrophy with inversion (turning inward) of the calcaneous (heel bone) and adduction (movement toward the midline) of the forefoot more marked on the left side (**D** and **E**). Such a severe clinical picture is characteristic of children with autosomal recessive CMT, either axonal or demyelinating, though it may occasionally occur in children with autosomal dominant or X-linked CMT.

walking, or foot deformity; in fact, they were able to do school gymnastics with no apparent trouble. This mild clinical presentation differs from that of autosomal recessive patients, either axonal or demyelinating, usually exhibiting prominent leg (Figure 1) or even hand amyotrophy (muscle wasting or atrophy). Be that as it may, the first two decades of life are an exceptional period of observation because a CMT1A clinical picture evolves appreciably more quickly

than in adult patients, where very slow progression of symptoms makes it difficult to assess the clinical course of the disease.

Clinical picture

The clinical picture in children with any type of CMT is similar and basically consists of a peroneal muscular atrophy syndrome (atrophy of muscles associated with the fibula bone) of variable severity. It is common to consider that clinical signs are more severe in CMT1 than in CMT2, but exceptions to this rule are not rare. Figure 2 illustrates frequency of clinical signs in our referred CMT1A children, splitting the series into three arbitrary age groups: 0 to 4 years (inclusion period), 5 to 10

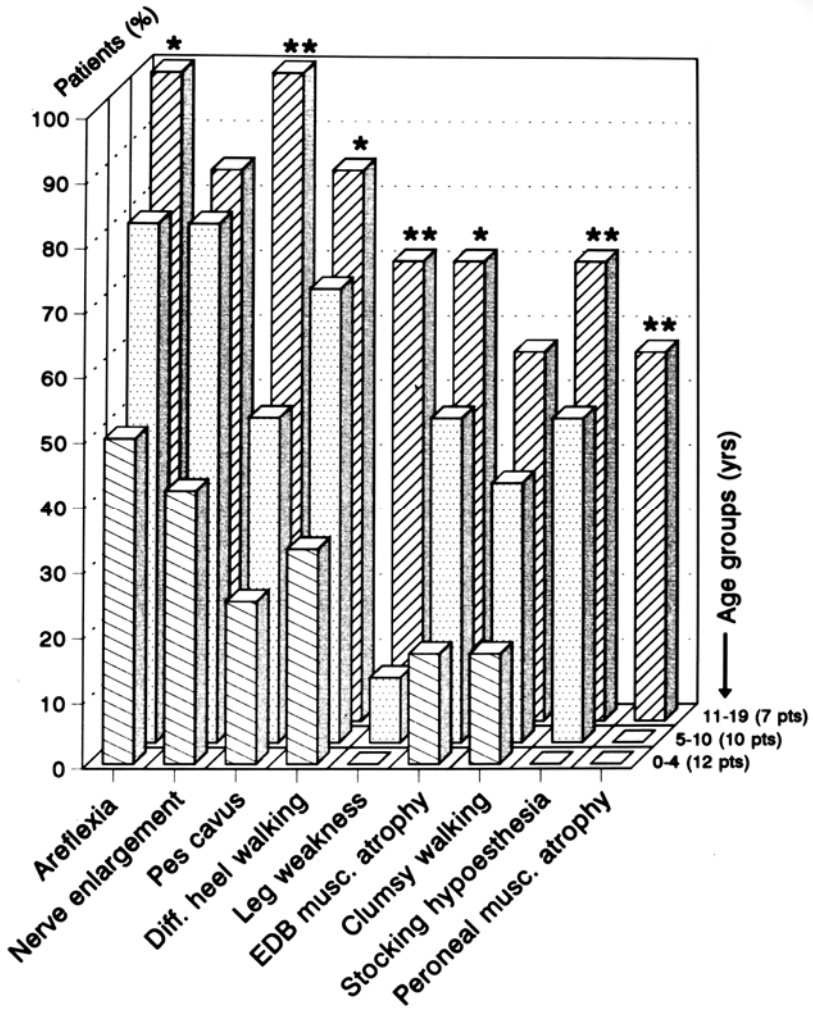

Figure 2. Frequency of clinical signs and symptoms in CMT1A children according to age groups. Asterisks indicate significant differences between older and younger groups (*p<0.05; **p<0.01). Reproduced with permission from: García A, Combarros O, Calleja J, Berciano J. Charcot-Marie-Tooth disease type 1A with 17p duplication in early infancy and childhood. A longitudinal clinical and electrophysiological study. *Neurology*. 1998; 50: 1061-1067.

years, and 11 to 19 years (in 1998). By definition, all 12 affected children were present in the youngest age group, but at the end of the study only 10 and 7 patients reached the required age to be included in the remaining groups.

During the inclusion period, the most frequent manifestations were areflexia, which is the absence of reflex (six cases), nerve enlargement (four cases), and difficulty in heel walking sometimes accompanied by shortening of tendo achillis (Achilles tendon) and incipient clawing of toes (Figure 3). Other signs observed included pes cavus, which is high arches (three

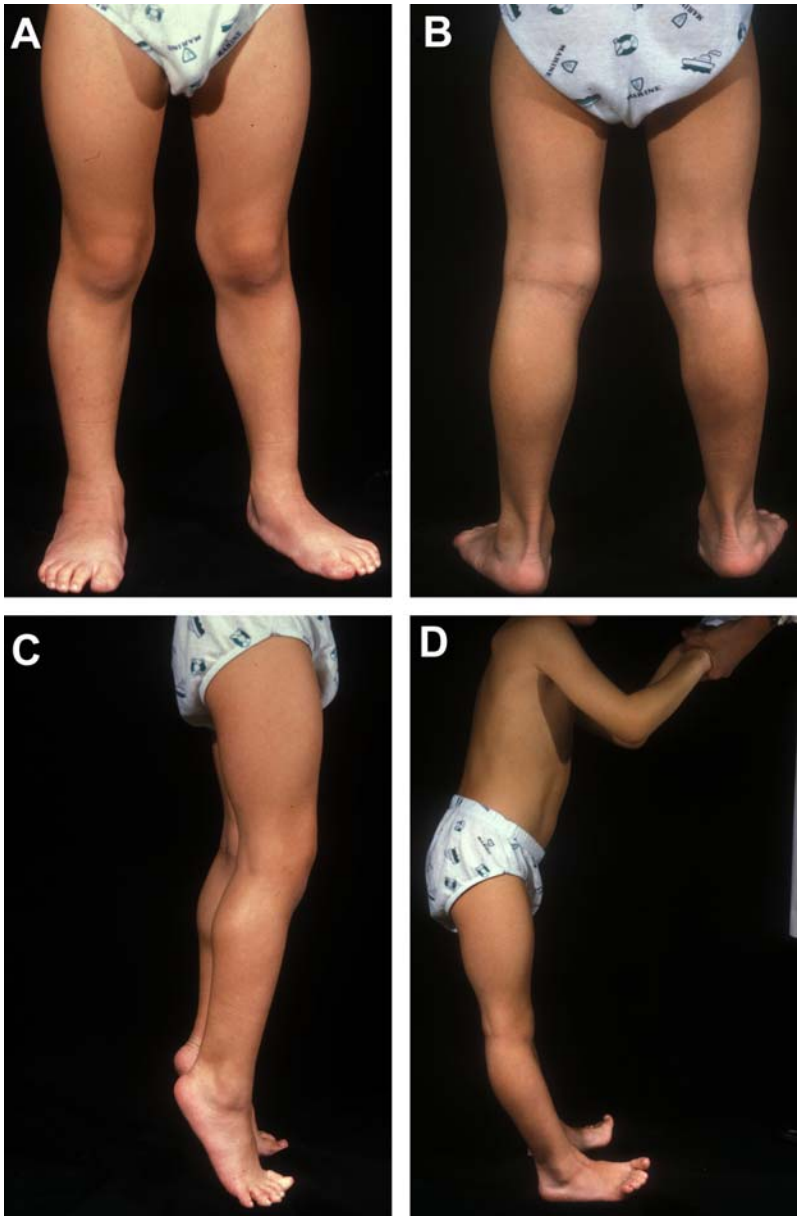

Figure 3. Affected CMT1A boy aged 5 years. (**A**) Neither peroneal muscular atrophy nor hammertoe can be observed. (**B**) Note prominence of Achilles' tendons. (**C**) There is no difficulty in standing on tiptoe. (**D**) Conversely, standing on the heels is not possible; note dynamic clawing of toes. Reproduced with permission from: Berciano J, García A, Combarros O. Initial semeiology in children with Charcot-Marie-Tooth disease. *Muscle Nerve.* 2003; 27: 34-39.

cases), pes planus, which is flat feet (three cases), and extensor digitorum brevis (EDB) muscle atrophy. In no case was leg muscle atrophy observed. Because of the difficulty in assessing sensation in small children, stocking hypoesthesia (decreased sensitivity in the area of the legs typically covered by stockings) was considered to be absent (see Figure 2). In the second age group (5-10 years), frequencies of all previous signs increased, areflexia, nerve enlargement (Figure 4) and difficulty in heel walking again being most frequent. Stocking hypoesthesia was now noted in half the patients. Once again, leg muscle atrophy was not observed. The above-mentioned triad of signs was almost constant in patients aged 11 years or more (see Figure 2). EDB muscle atrophy was an outstanding sign in some patients, and for the first time incipient to moderate atrophy of antero-lateral leg compartments was observed (four cases). Significant percentages of clinical signs of this and the youngest group appear in Figure 2. Two children with pes planus at first examination then exhibited pes cavus.

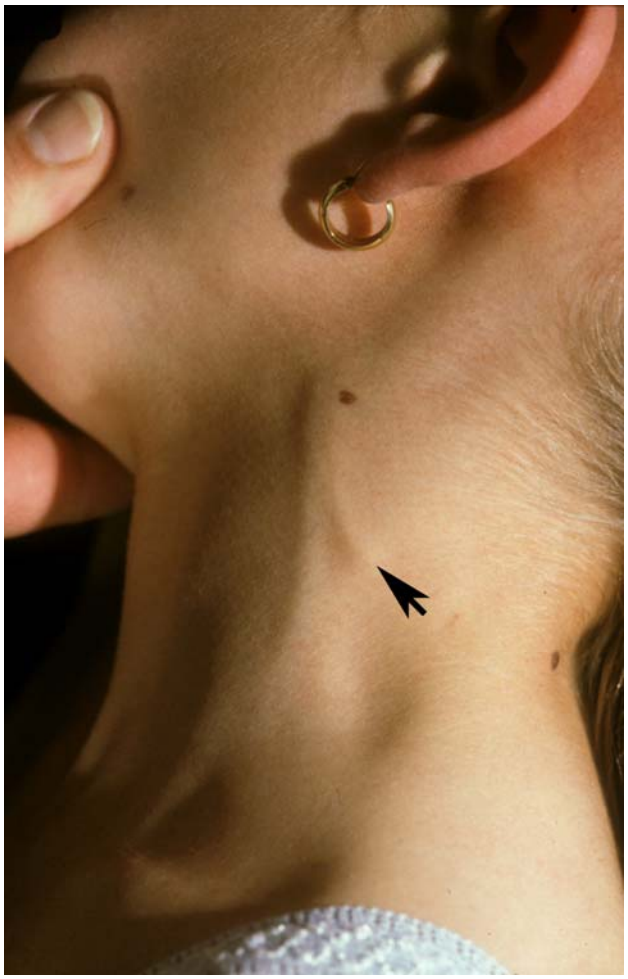

Figure 4. The great auricular nerve is visibly enlarged (arrow) in this CMT1A girl aged 8 years.

Pathophysiology

In the longitudinal study in CMT1A children, we investigated the

electrophysiologic abnormalities accounting for the appearance and progression of EDB atrophy. All patients had two or more electrophysiological studies of the peroneal nerve. EDB atrophy was observed in 2 of 12 (17 percent) by age 5, in 8 of 10 (80 percent) examined between 5 and 9 years, and in all eight patients (100 percent) who had reached the second decade at the end of the study. Nerve conduction maturation was systematically abnormal, but by age 5, the mean values of nerve conduction parameters of peroneal nerve did not significantly differ from those in older patients. Compound muscle action potential (CMAP) amplitudes of EDB were reduced in 42 percent of cases initially and 100 percent upon last exam. Furthermore, a constant finding throughout the study was progressive reduction of CMAPs, these becoming unobtainable in four cases. We concluded that EDB muscle atrophy in CMT1A children is an age-dependent sign, which is accounted for by gradual reduction of the distal peroneal nerve CMAP amplitudes, not to the degree of slowing of motor conduction velocity, that is, the degree of secondary axonal degeneration to demyelination.[9,11]

Pes cavus deformity in CMT, a cardinal manifestation of the disease, is defined as pes cavus secondary to a plantar flexion deformity of the first metatarsal, with no contribution to the cavus deformity by a dorsiflexion deformity of the calcaneus.[12] The theories of pathogenesis of pes cavus involving muscle balance fall into two main categories: those involving the intrinsic muscles of the foot and those involving the muscles of the leg. The role of the intrinsic foot muscle in the etiology of pes cavus is difficult to decide upon and opposing theories exist.[12] In fact, most authors agree with the contention that pes cavus in CMT results from an imbalance between the peroneus longus and its antagonist, the tibialis anterior. Such a contention, however, derives from studies including CMT proband cases with evident weakness of peroneal musculature, and not from series analysing secondary cases in early stages of the clinical course, where foot deformities occur with no evidence of leg muscle weakness.[8,10]

We addressed this question by performing standardized clinical and magnetic resonance imaging (MRI) studies of leg and foot musculature in 11 CMT1A patients, including three aged between 8 and 17 years.[13] Functional disability scale (FDS) for disease severity in terms of ability to run or walk (ranging from 0 [normal]to 8 [bedridden] points) and CMT neuropathy score (CMTNS) (ranging from mild [CMTNS ≤ 10 points] to severe [CMTNS 21-36 points]) were administered. We found that clinical-MRI patterns of lower limb amyotrophy vary with evolution of symptoms. Selective involvement of intrinsic foot muscles is the characteristic pattern of CMT1A cases with minimal disease signs (Figures 5-7), namely, with no peroneal

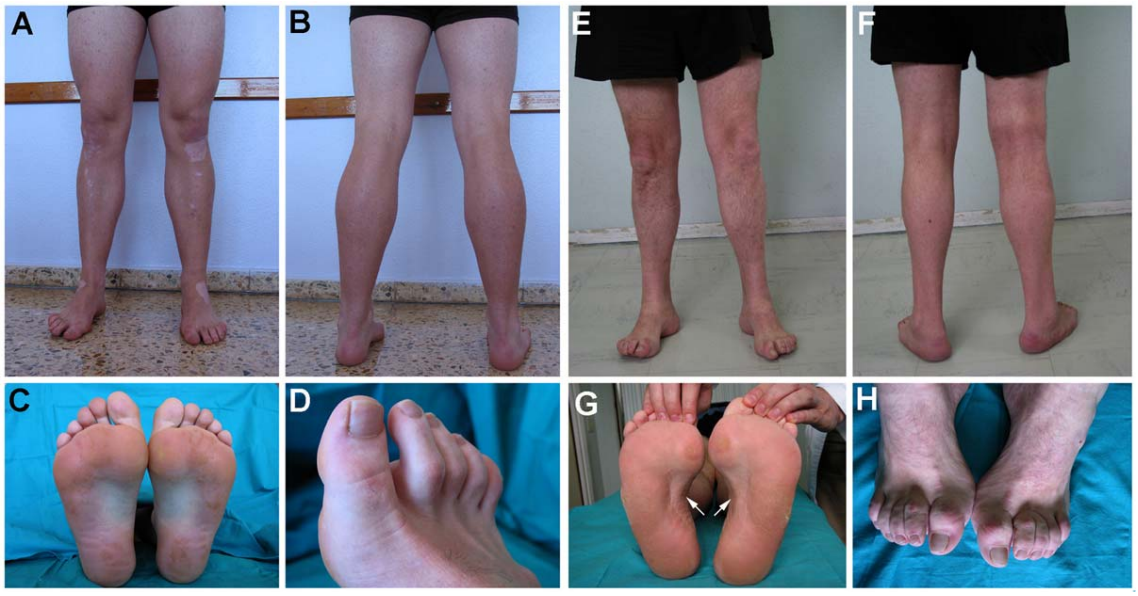

Figure 5. Pictures of two CMT1A patients aged 17 years (**A-D**; FDS = 0; CMTNS = 2) and 41 years (**E-H**; FDS = 2 [inability to run]; CMTNS = 12 [moderate disease]). (**A**, **B**) Note the absence of leg amyotrophy. (**C**, **D**) Close up pictures of the feet illustrating moderate pes cavus, and toe clawing that almost disappears during standing up (**A**) indicating its reducible nature. (**E**, **F**) Note the presence of peroneal muscular atrophy, toe clawing and marked varus deformity of the ankles. (**G**, **H**) Close up pictures of the feet showing severe pes cavus and varus, toe clawing and atrophy of abductor hallucis muscles (arrows). Reproduced with permission from: Gallardo E, García A, Combarros O, Berciano J. Charcot-Marie-Tooth disease type 1A duplication: spectrum of clinical and magnetic resonance imaging features in leg and foot muscles. *Brain.* 2006; 129: 426-437.

muscular weakness as described in the two younger age groups in Figure 2. Afterwards this pattern usually combines a variable and predominantly distal involvement of leg muscles (Figures 5, 7 and 8). The predominant atrophy of intrinsic foot muscles and distal portions of leg muscles observed here concurs with the proposal of a length-dependent degeneration of motor axons as the mechanism of muscle denervation in CMT1A.[9,11]

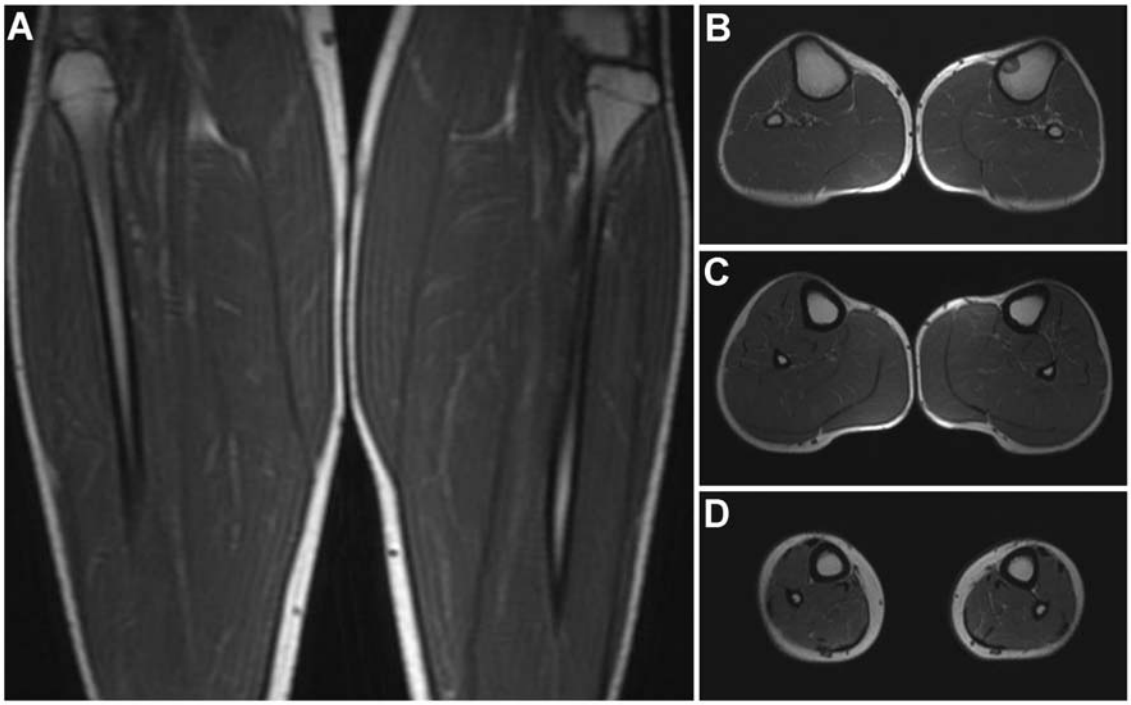

Figure 6. Coronal (**A**) and axial (**B**, proximal calves; **C**, mid calves; and **D**, lower calves). T1-weighted images from the patient illustrated in **Figure 5A-D** showing that all four leg compartments are preserved. Reproduced with permission from: Gallardo E, García A, Combarros O, Berciano J. Charcot-Marie-Tooth disease type 1A duplication: spectrum of clinical and magnetic resonance imaging features in leg and foot muscles. *Brain.* 2006; 129: 426-437.

Furthermore, our findings give support to the notion that forefoot cavus is initiated by selective weakness of intrinsic foot muscles.[10,14] The first event would be atrophy and weakness of the lumbricals and other intrinsic foot muscles causing dorsiflexion of metatarsophalangeal joints, initially manifested as clawing of the toes

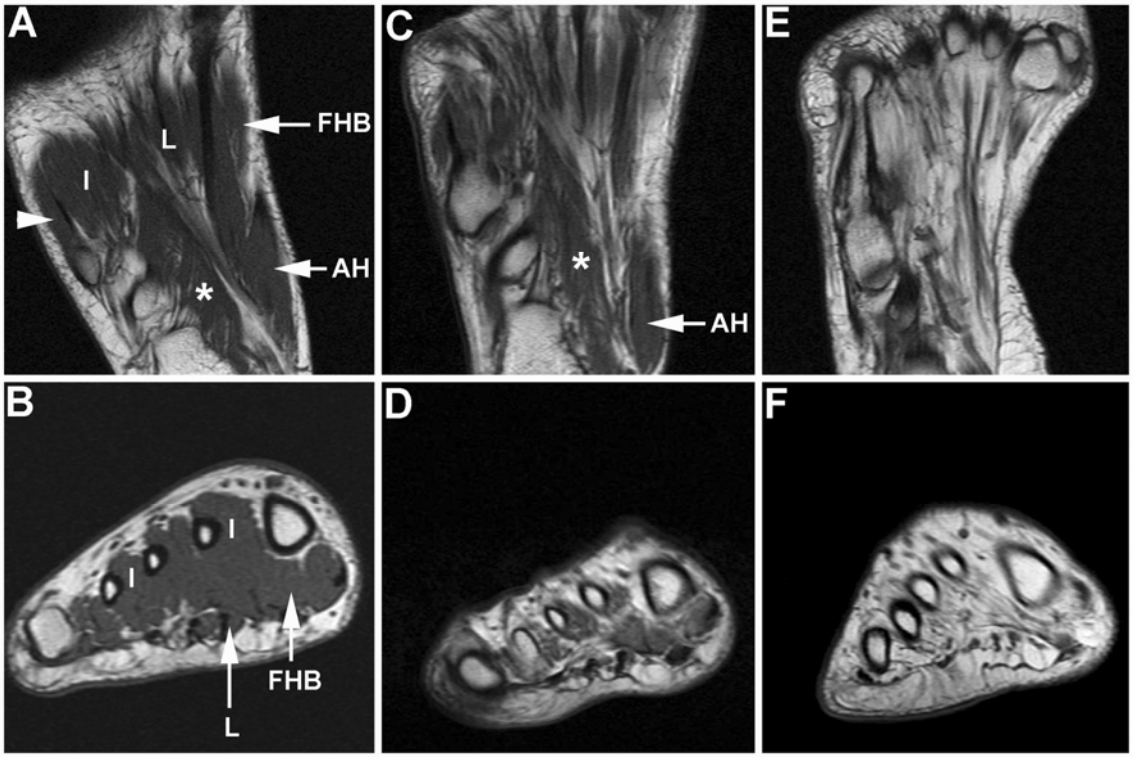

Figure 7. T1-weighted images of intrinsic foot muscles in a control subject (**A**, **B**), and in cases illustrated in **Figure 5** (patient aged 17 years, **C** and **D**; patient aged 41 years, **E** and **F**) obtained at the same levels in the long and short foot axes. (**A**) Normal identified muscles in this axial section include flexor hallucis brevis (FHB), lumbricals (L), abductor hallucis (AH), and flexor digitorum accesorius (asterisk); interossei (I) and flexor digiti minimi brevis (FDMB, arrowhead) are partially visualized. (**B**) Normal muscles clearly identified in this coronal section include interossei (I), lumbricals (L) and FHB. (**C**, **D**) Note evident but not complete fatty infiltration of the lumbricals, FHB, FDMB and interossei; AH and flexor digitorum accesorius (asterisk) are relatively preserved. (**E**, **F**) Compared with the previous case, note massive fatty infiltration of all mentioned foot muscles. Reproduced with permission from: Gallardo E, García A, Combarros O, Berciano J. Charcot-Marie-Tooth disease type 1A duplication: spectrum of clinical and magnetic resonance imaging features in leg and foot muscles. *Brain.* 2006; 129: 426-437.

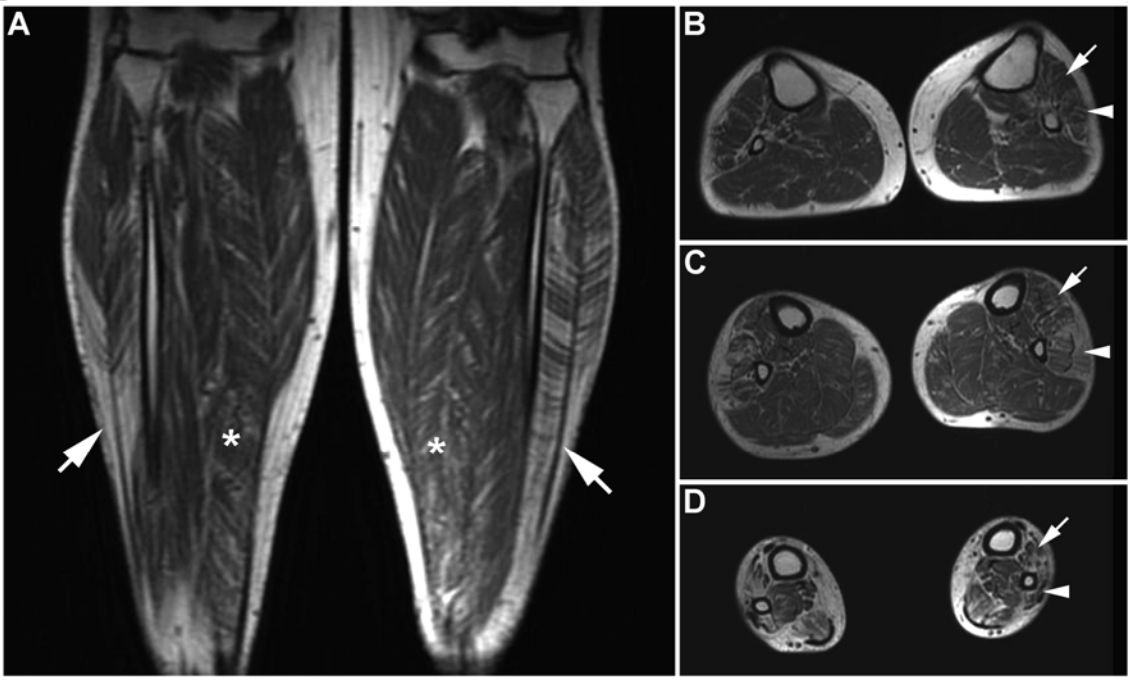

Figure 8. MRI study from the patient illustrated in **Figure 5E-H**. (**A**) Coronal T1-weighted image of the legs showing extensive and striped fatty infiltration of peroneal muscles, which is distally accentuated (arrows). Distal soleus muscles (asterisks) are involved to a lesser degree. Axial T1-weighted images (**B**, proximal calves; **C**, mid calves; and **D**, lower calves) showing distally accentuated fatty infiltration of the lateral (arrowheads) and anterior (arrows) muscle compartments. There is also fatty infiltration of the soleus muscles (**D**), but other muscles of the superficial and deep posterior compartments are preserved. Reproduced with permission from: Gallardo E, García A, Combarros O, Berciano J. Charcot-Marie-Tooth disease type 1A duplication: spectrum of clinical and magnetic resonance imaging features in leg and foot muscles. *Brain.* 2006; 129: 426-437.

and flattening of the transverse arcus plantaris. During gait, prior to toe-off, as metarsophalangeal joints extend, the plantar aponeurosis is wrapped around the metatarsal heads and the short flexors contract, approximating the pillars of the longitudinal arch and shortening the Achilles tendon that limits ankle dorsiflexion. Therefore, initial foot deformities and walking difficulties correlate with abnormal foot architecture due to selective denervation of the intrinsic foot muscles.[14] In more advanced stages of the disease, foot deformities are accompanied by weakness of peroneal musculature

and hence muscle imbalance may play here a pathophysiological role in walking and foot semeiology.

Diagnosis

Diagnosis relies on clinical picture, mode of transmission and electrophysiological evaluation. Electrophysiological examination should include the maximum possible number of the affected individual's relatives. Under such circumstances, is usually possible to establish the type of inheritance and if we are confronted with an axonal or demyelinating CMT disorder. This is an essential step to guide molecular testing. Nerve biopsy is no longer a routine diagnostic test, being now reserved for cases with no well defined phenotype or for doubtful cases where differential diagnosis with other polyneuropathic syndromes is necessary.

Treatment

Treatment is at present symptomatic with a multidisciplinary approach, including pediatricians, neurologists, physiotherapists, and orthopedists. In most children affected with CMT, the disease initially is just the expression of altered foot architecture due to denervation of intrinsic foot musculature, with no real leg muscle weakness; this calls for a conservative management. Children should be encouraged to remain as active as possible.

Over-expression of PMP22 in rodents has created animal models that closely mimic CMT1A duplication.[15] In 2003, it was demonstrated that transgenic rats over-expressing PMP22 worsen with progesterone administration, a known promoter of PMP22 expression, and improve when treated with a progesterone antagonist, onapristone.[16] Currently available progesterone antagonists, including onapristone, are not suitable as treatments for CMT1A because of unacceptable side effects. More recently, treatment with ascorbic acid, a known promoter of myelination, has been tried in a mouse model over-expressing PMP22.[17] The results

show a convincing clinical and pathological improvement in this animal CMT1A phenotype. The potential therapeutic role of ascorbic acid in CMT1A patients was addressed in the 136th ENMC International Workshop on Charcot-Marie-Tooth disease type 1A (8-10 April 2005, Naarden, The Netherlands); it was concluded that a trial of ascorbic acid in CMT1A is warranted and feasible, a protocol and core outcome measures now being available for an immediate international trial. Another therapeutic alternative might be neurotrophin-3, which augments nerve regeneration in animal models of CMT1A .[18]

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Orthopedic Considerations for Charcot-Marie-Tooth Disorders

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This chapter focuses on the orthopedic complications associated with Charcot-Marie-Tooth (CMT) disorders. In general, the orthopedic manifestations of CMT reflect the severity of neurological involvement and subsequent muscle weaknesses. Due to the progressive nature of this condition, the severity of symptoms is a time-dependent phenomenon. Generally, the age of onset of clinical signs and symptoms is a good prognostic predictor of outcome. The younger the patient is when signs and symptoms begin to manifest, the greater the probability that they will develop more significant orthopedic complications as the result of CMT. Full clinical expression is usually complete by the third decade.[1] Interestingly, neither the type of CMT, nor the degree of orthopedic problems experienced by other members of the same family, including homozygous twins, can predict how the disease will progress and afflict an individual. The salient orthopedic features of patients with CMT involve mainly the hands and feet. However, mild *scoliosis* (a sideways curvature of the spine), *kyphosis* (an outward curving of the spine in the chest area), *kyphoscoliosis* (a combination of kyphosis and scoliosis) and *hip dysplasia* (dislocation of the hip joint) may also develop.

The Foot and Ankle

Foot and ankle manifestations are among the earliest clinical signs of CMT. *Bilateral* (affecting both the left and the right side of the body) cavovarus feet (Figure 1), which are high-arched feet, is the most common foot deformity associated with CMT.[2,3] However, approximately 10-15 percent of patients with CMT may present with bilateral *pes planus* feet deformities (flat feet). The foot deformities may be asymmetric. The severity of foot and ankle involvement is quite variable.

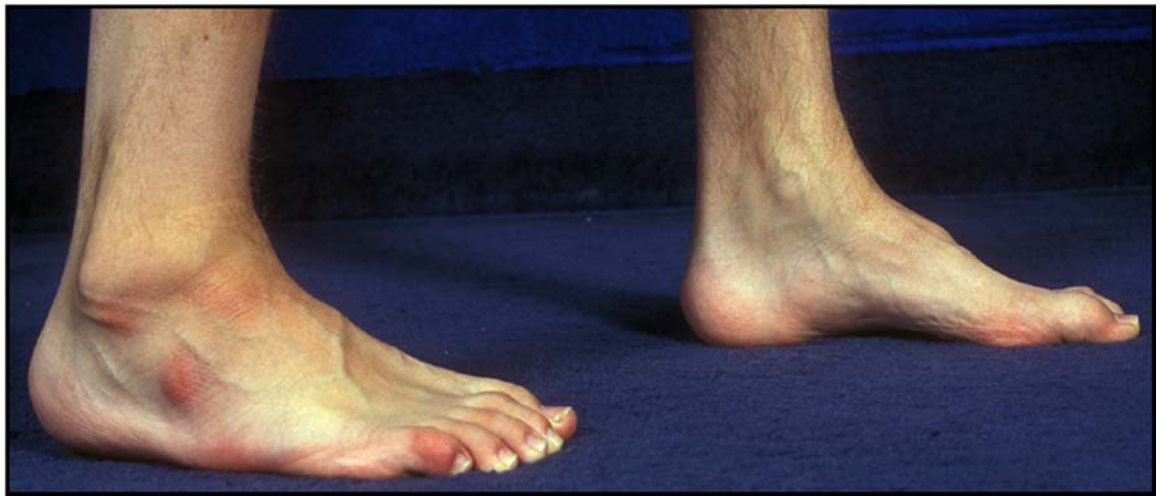

Figure 1. Fourteen year old boy diagnosed with CMT1 presenting with bilateral cavovarus feet.

Bilateral cavovarus feet are seldom present at birth, but gradually become apparent as the child's feet grow and mature.[4] Most children are brought to the physician for evaluation of recurrent ankle sprains, frequent falls, a swaying gait and an awkward running gait, ankle pain with standing and activity, cosmetic deformity, and/or difficulty with shoe wear. Some patients have asymptomatic feet and the clinical observation of bilateral cavovarus feet is an incidental finding. Although there are many possible causes of bilateral cavovarus feet,[5] the most common etiology is CMT. Nagai, et al.,[6] reported that the probability that a patient with bilateral cavovarus feet is diagnosed with CMT; regardless of family history, is 78 percent. A family history

Table 1. Motor Imbalance and Deformity

	Weak Muscle	Strong Muscle	Deformity
Hindfoot	**Peroneus Brevis**	**Tibialis Posterior**	***Hindfoot varus*** (hindfoot angled inward)
	Tibialis Anterior	**Achilles Tendon Contracture**	***Equinus*** (loss of flexibility in the calf and Achilles tendon)
Midfoot		**Contracture of the Plantar Aponeurosis** Origin: *calcaneus* (heel bone) Insertion: onto the fibrous digital sheaths distally	**Accentuated *Windlass mechanism*** (The Windlass mechanism is the coordinated action of foot muscles, tendons, ligaments and bones to maintain arch height and foot rigidity. Incorrect Windlass function prevents, the foot from acting as an efficient lever and effective push off power cannot be achieved.) **Hindfoot varus** **Midfoot cavus** **Claw toes**
Forefoot	**Tibialis Anterior**	**Peroneus Longus**	**Plantar flexed first metatarsal** ***Forefoot valgus*** (forefoot angled outward) ***Steppage gait*** (a high lifting of the advancing foot so that the toes clear the ground) and ***foot drop*** (weakness in the muscles of the foot and ankle, which interferes with a person's ability to flex the ankle and walk with a normal heel-toe pattern)
	Intrinsics (muscles located within the foot and cause movement of the toes, such as. flexors, extensors abductors, and adductors of the toes; several intrinsic muscles also help support the arches) **Tibialis Anterior**	**Toe Extensors** (Extensor Hallucis Longus, Digitorum Longus)	**Claw toes** ***Ankle dorsiflexion*** (foot bending upward from the ankle)

of CMT increases the probability to 91 percent. It is recommended that all patients with bilateral cavovarus feet, regardless of severity or symptoms, especially with a known family history, be investigated for CMT.

Clinical Presentation and Examination

Patients frequently present to the physicians office complaining of recurrent ankle sprains, *metatarsalgia* (pain in the forepart of the foot), *claw toes* (toes that contract at the middle and end joints), pes cavus and/or a tarsal prominence. Because CMT tends to affect the longest nerves to the smallest muscles first, patients will present with clinical findings in their feet before their hands are affected.

Table 2. Characteristic Physical Exam Findings

	Clinical Appearance
Hindfoot	• Varus deformity • *Callosities* (thickened skin) under the lateral aspect of the heel
Midfoot	• Cavus (high arch when weight bearing) • Callosities along the lateral border of the foot
Forefoot	• Callosities under the base of the fifth metatarsal, metatarsal heads, particularly the first metatarsal head • Plantar flexed first metatarsal • Equinus • Claw toes with dorsal toe irritation • Valgus deformity

The simplest way to examine the cavovarus foot and to understand the pathophysiology and treatment of the cavovarus foot deformity in CMT is to divide the foot into three main components: the hindfoot, the midfoot and the forefoot. All of the three aforementioned components are affected by the disease process. The deformity seen is reflective of the underlying motor imbalance around the foot and ankle (Table 1).[1,7] A summary of characteristic physical examination findings is shown in Table 2. In addition to these

findings, calf muscle atrophy may be present.

Radiographic Evaluation

Standard weight-bearing *AP* (anteroposterior, or, from the front to the back) and *lateral* (from the side) radiographs of the feet should be obtained at the initial office visit for any patient presenting with bilateral cavovarus feet, regardless of their clinical history. The cavovarus foot can be defined by changes seen on the lateral radiograph, an increase in the talar-first metatarsal angle (Meary's Angle), an increase in *calcaneal pitch* (a measurement of the angle of an imaginary line drawn from the top of the arch to the base of the heel); and an increase in the calcaneus-first metatarsal angle (Hibb's Angle) (Figure 2).

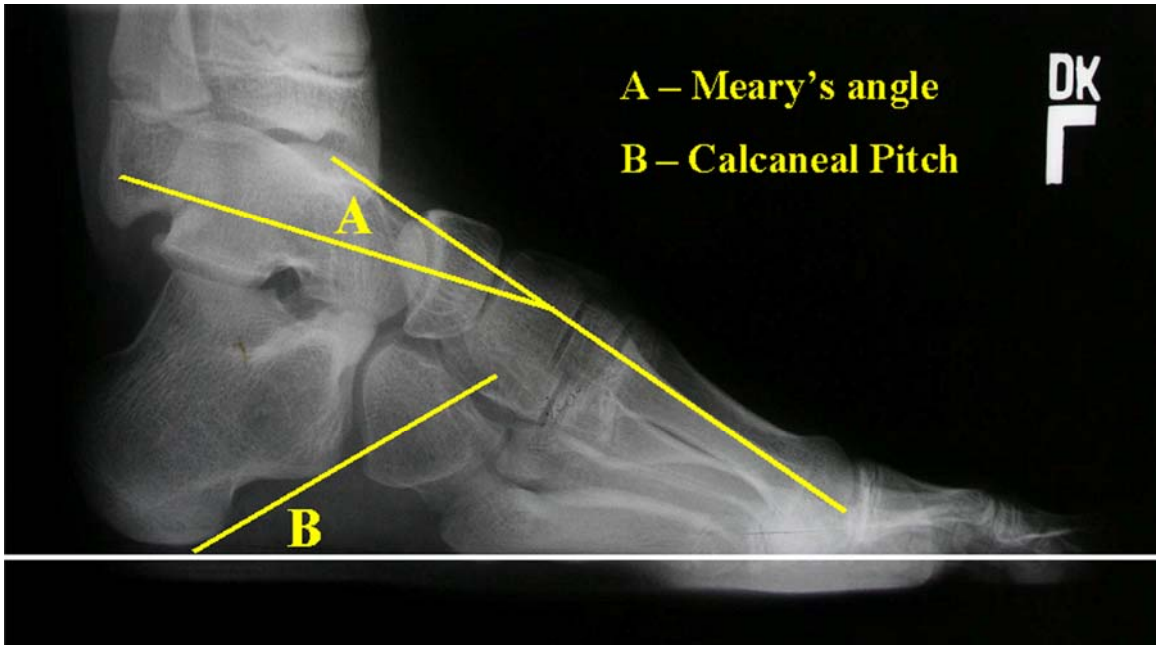

Figure 2. Lateral radiograph showing increase in the talar-first metatarsal angle (Meary's Angle) and an increase in calcaneal pitch.

In 2005, Azmaipairashvilli, et al.,[8] described a new radiographic method to evaluate the flexibility of the hindfoot. This lateral radiographic view is called the Coleman Block View, which is based upon the Coleman Block Test. The foot is placed on a radiolucent

block; the first, second and third rays are allowed to drop down (Figure 3). Restoration of the talar dome and the length of the *os*

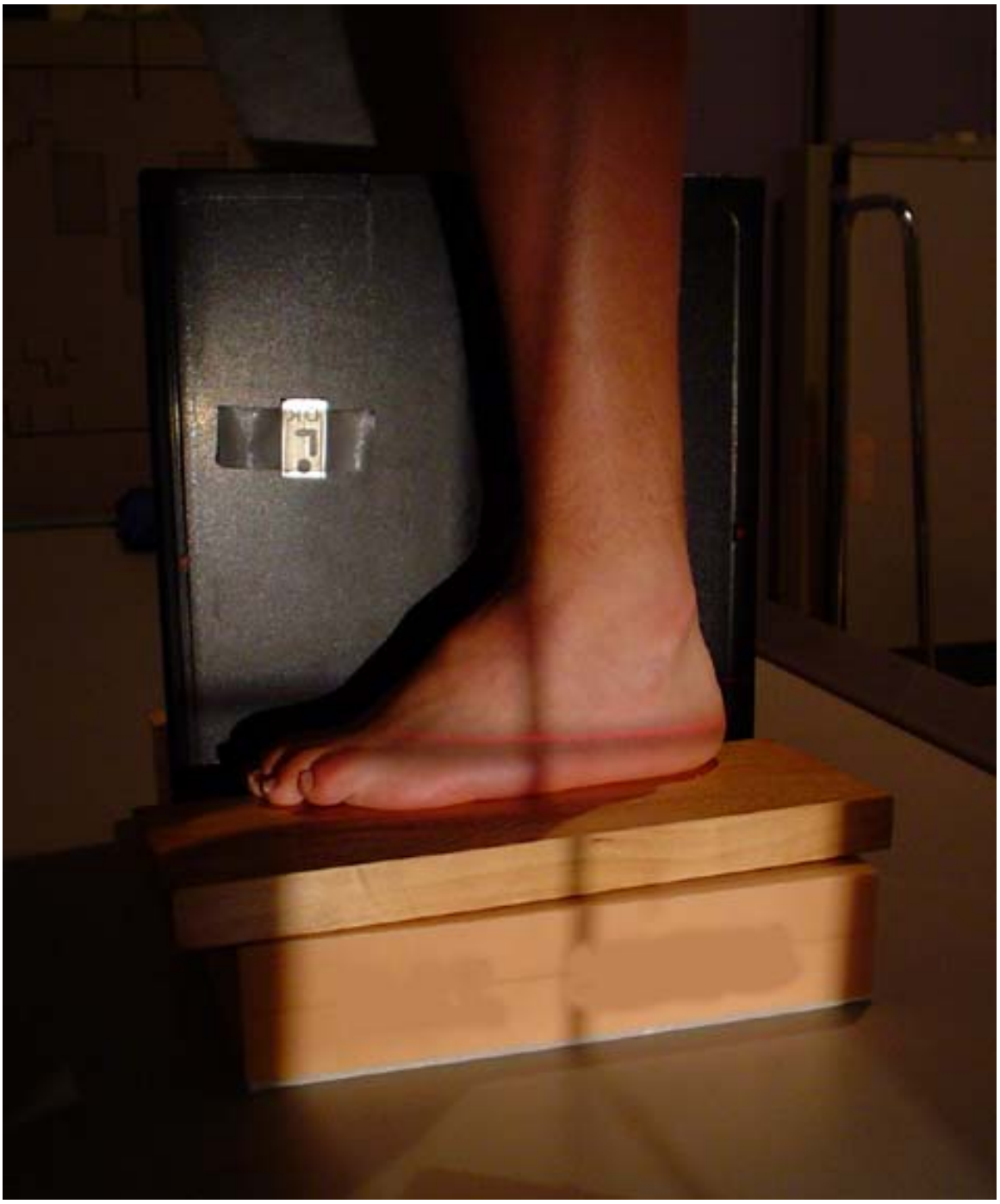

Figure 3. Clinical photograph demonstrating the Coleman Block view.

calcis (heel bone) documents flexibility of the hindfoot (Figure 4A and 4B). The Coleman Block View must be obtained pre-operatively because it directs operative treatment decisions.

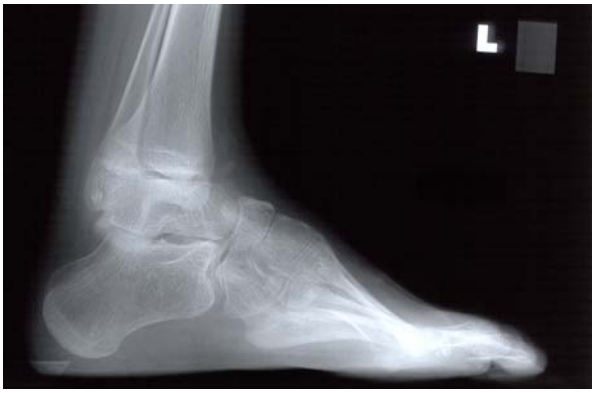

Figure 4A. Standard lateral weight bearing radiograph demonstrating cavovarus feet.

The Hand

Upper extremity involvement is seen in one-half to two-thirds of patients affected by the condition.[9] Onset of symptoms in the upper extremity occurs later when compared to the lower extremity, with hand symptoms occurring at 19 years of age on the average.[10] Both motor and sensory changes occur in CMT. The patterns and progression of both motor and sensory changes were found to be both consistent and predictable. The hand initially presents with loss of power of the intrinsics and forearm atrophy. Clawing of the hands is seen with involvement of the ring and small digits occurring first. Neurologic deficits are usually consistent with median and ulnar nerve distribution. The majority of patients with CMT will develop hand and upper extremity symptoms; however, only few will ultimately require surgery because many develop adaptive mechanisms and remain functional.

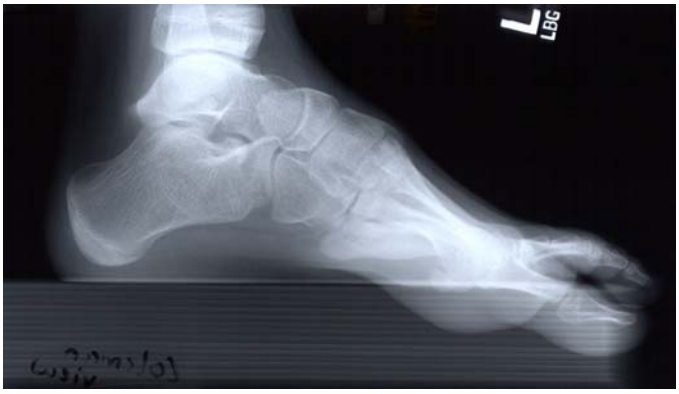

Figure 4B. Coleman Block view showing hindfoot flexibility and restoration of the talar dome and the length of the os calcis.

The Hips

In 1985, Kumar, et al.,[11] published the index report associating CMT with the development of neuromuscular *acetabular dysplasia* (dislocation of the thigh bone where it meets the acetabular socket of the hip) and hip *subluxation* (partial dislocation) occurring in the second or third decade of life. In 1994, Walker, et al.,[12] attempted to determine the prevalence of acetabular dysplasia and hip subluxation in the CMT population. Only 8 percent of the patients (n=74) reviewed had radiographic evidence of acetabular dysplasia and hip subluxation.

Clinical Presentation and Evaluation

Acetabular dysplasia and hip subluxation are usually asymptomatic until adolescence.[11,13] These patients rarely complain of hip or knee pain and will most likely present with subtle changes in their gait pattern. A subtle sway or *Trendelenberg gait* (to overbalance or slip to one side when that foot is raised off the ground) may be present.

The development of acetabular dysplasia and hip subluxation during adolescence has been attributed to the progressive development of motor weakness caused by the underlying peripheral neuropathy. The development of Trendelenberg gait may be the first sign of muscle weakness about the hips. The weak hip abductors and extensors are unable to counter the effects of the stronger hip adductors and flexors. The motor imbalance alters the forces crossing the hip joint and leads to the development of a *valgus anteverted femoral neck* (the upper part of the thigh bone is turned forward and outward where it meets the hip bone), hip subluxation and acetabular dysplasia. Ultimately, the patient will complain of hip pain as degenerative changes in the hip joint develop.

Radiographic Evaluation

All patients with CMT require a standard standing AP pelvis radiographic exam performed at their initial presentation, regardless

of clinical and physical examination findings. Acetabular dysplasia and possibly subluxation of the femoral head may be seen on radiographs before the onset of clinical symptoms (Figure 5). Late radiographic changes include signs of degenerative joint disease.

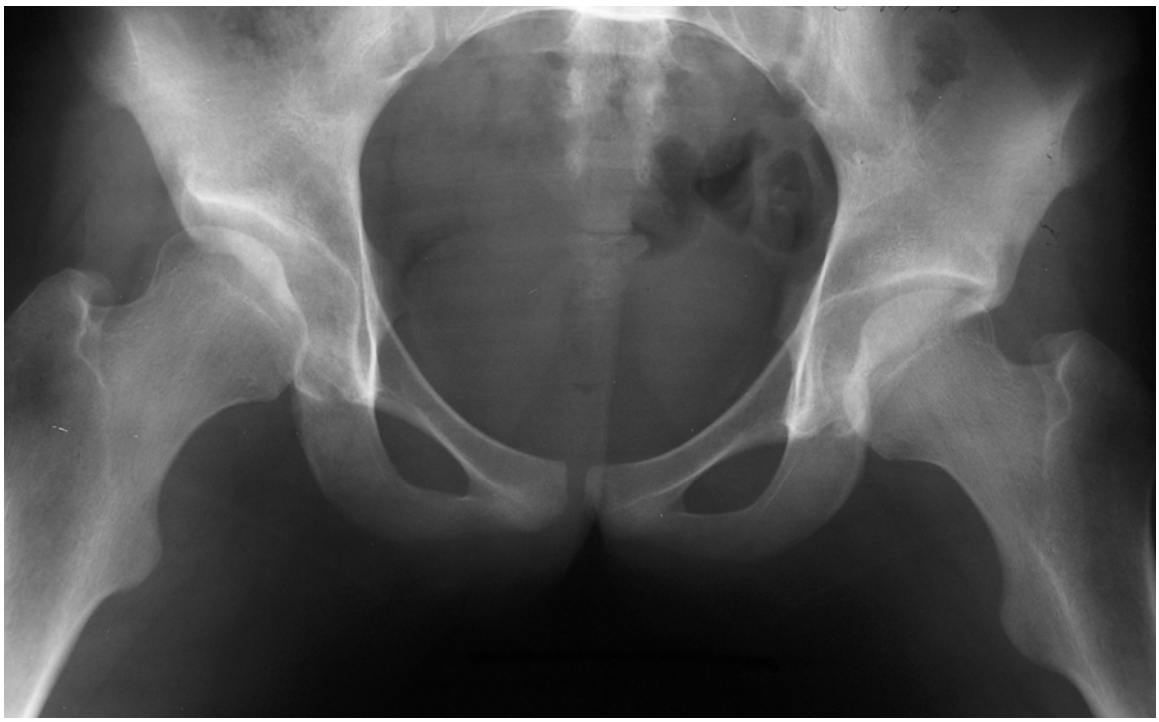

Figure 5. 15 year-old child diagnosed with CMT1 who has dysplasia of the right hip.

When changes are seen on plain radiographs, a CT-scan, including a 3-D reconstruction should be obtained to quantify the degree of acetabular dysplasia and define the rotational deformities in the femur.

The Spine

The incidence of scoliosis amongst adolescents with CMT is 37 percent.[14] Adolescent females with CMT, especially those with CMT1, are at increased risk of developing scoliosis. Neither the prognosis of curve progression in adults with CMT nor the risk of adult scoliosis is known.

Clinical Presentation and Evaluation

All patients with CMT should be screened for scoliosis. Similar to idiopathic scoliosis, the development of spine deformity occurs just prior to the onset of puberty (10 years of age to skeletal maturity). Pain is usually not the presenting symptom. The presenting complaint is usually related to a change in the patient's physical appearance.

The curve patterns (right thoracic) and location of the curve are similar to those observed in adolescent *idiopathic* (of unknown origin) scoliosis. In the *sagittal plane* (the division of the body from left and right), the scoliotic portion of the spine is typically *lordotic* (curved forward) in adolescent idiopathic scoliosis. In adolescents with CMT, the scoliotic portion of the spine in the sagittal plane is typically *kyphotic* (curved backward).[15] Neurological deficits other than those characteristic of CMT are rare.

An atypical presentation of idiopathic scoliosis requires an immediate work-up for spinal cord pathology. This includes, < 10 years of age, a left thoracic curve, rapid progression of the scoliosis and/or large curve at initial visit, recurrent back and neck pain, headaches, an ataxic gait, rapid progression of foot deformities, and new onset of muscle weakness affecting those muscles that are typically spared in CMT or progressive weakness of the affected muscles.

Radiographic Evaluation

The initial evaluation should include a three-foot standing *PA* (posteroanterior, or, from back to front) and lateral radiographic view of the spine. Repeat radiographs should be obtained at each subsequent follow-up visit to monitor the progression of the curve. An increase in the magnitude of the curve of 6 degrees or more represents progression of the curve. This is the same criteria used to monitor curve progression in adolescent idiopathic scoliosis.

Treatment

Foot and Ankle

Conservative treatment of the cavovarus foot includes, physical therapy, night time splinting, shoe wear modifications and the use of *orthotics* (devices that support or supplement weakened or abnormal joints or limbs). Physical therapy is important in the management of foot problems. Nightly stretching and strengthening exercises may help to decrease foot pain and the incidence of recurrent ankle sprains by maintaining flexibility and increasing or maintaining the strength of the muscles. Night-time splinting should be encouraged to prevent the development of an equinus contracture.

Shoe wear modifications include the use of high top shoes or boots to improve stability, and extra depth toe boxes may decrease the irritation on the dorsum of the claw toes. The use of orthotics is also recommended to alleviate foot pain. Orthotics such as the University of California, Berkeley (UCB), a full length shoe insert, or a lightweight polypropylene ankle foot orthosis (AFO) may be used, depending on the needs of the patient. Orthotics may benefit the patient with a flexible cavovarus foot deformity. The goal of the orthotic is to control the position of each component of the foot, holding it in neutral position, and, therefore, correcting or decreasing the abnormal pressure points on the plantar surface of the foot. An AFO may also be used to support a dropfoot and to decrease the energy expenditure of a steppage gait. Orthotic devices also help to protect the *insensate foot* (a foot with a lack of sensation) from injury. When all conservative measures have been exhausted, surgical treatment options may be entertained.

Surgical treatment decisions are dictated by the age of the patient and by the flexibility of the foot deformity. The foot is divided up into its three main components, the hindfoot, midfoot and forefoot. A Coleman Block Test and a Coleman Block View must be performed

pre-operatively. Surgical recommendations are based upon the results of these tests (Table 3).

Table 3. Surgical recommendations

Age	Forefoot	Hindfoot	Surgical treatment
8 – 12 years	Flexible	Flexible	Soft tissue only
> 12 years	Flexible	Flexible	• Soft tissue • First MT/medial *cuniform osteotomy* (a wedge-shaped surgical division) • +/- midfoot *osteotomy* (surgical division)
> 12 years	Stiff	Flexible	• Soft tissue • Midfoot osteotomy
> 12 years	Stiff	Stiff	• Soft tissue • First MT/medial cuniform osteotomy • Midfoot osteotomy • *Calcaneal* (heel bone) osteotomy

Only soft tissue surgical procedures should be performed in pediatric patients under the age of 12 years and in those who are skeletally immature. It is preferable that bony procedures, such as osteotomies and *arthrodesis* (the surgical fixation of a joint, or fusion), be performed in skeletally mature individuals. In skeletally mature patients with severe deformities, a triple arthrodesis may be used; however, long-term studies have shown that these procedures predispose the patient to the development of degenerative arthritic changes.[16,17]

Hand

The goal of treatment of the hand and upper extremity is to maintain function. Conservative measures such as physical therapy and splinting may be used to help stretch and prevent contractures. Another option is to use adaptive devices to aid with activities of daily living. Specific functional problems may also be treated surgically.

These problems include lack of opposition, weak pinch, and finger clawing.[18] These problems may be addressed by performing tendon transfers to correct loss of function and increase strength. Joint instability may be treated with an arthrodesis to stabilize the unstable segments. Finger clawing can be treated by looping the flexor digitorum profundus muscle around the A1 pulley as described by Zancolli.[18] However, prior to performing any surgical correction, a thorough electrodiagnostic evaluation of the upper extremity is advised to help identify and select the optimal muscles for transfer.[19]

Spine

The treatment of scoliosis in patients with CMT does not differ from that described for adolescent idiopathic scoliosis.[20] Should brace therapy fail and a posterior spine fusion is required, neurological monitoring in these patients is difficult. Because of the peripheral neuropathy, *SSEP* monitoring (Somatosensory Evoked Potential, a test that shows the electrical signals of sensation going from the body to the brain) of somatosensory-evoked potentials may be impossible.[21] An attempt should be made to use *motor-evoked potentials* (MEPs). The gold standard is to perform an *intraoperative wake-up test* (the patient is awakened during the operation to test nerve conduction).

Hip

An infant born into a family with a history of CMT should have normal hips at birth. If the hips are found to be dysplastic, then these are probably congenital in nature and should be treated as developmental dysplasia of the hip (DDH).[22] All adolescents with CMT, regardless of symptoms, should have baseline AP pelvis radiograph to rule out early acetabulum and hip changes. Follow-up AP pelvis radiographs should be obtained at least once every two years. Neuromuscular hip dysplasia is a dynamic problem and once present will progress unless treated surgically. If left untreated, degenerative changes will occur and ultimately the patient may require a total hip *arthroplasty* (joint replacement).

Physical therapy plays a key role in the peri-operative management of neuromuscular hip dysplasia. To prevent injury and to improve post-operative rehabilitation, it is imperative that these patients maintain full hip range-of-motion and optimize the strength of the hip abductors and extensors. An overall body conditioning program is also important. These factors ultimately influence the outcome of reconstructive surgery for the hip and acetabulum. There is no role for bracing in neuromuscular hip dysplasia.

Once radiographic evidence of acetabular dysplasia and/or subluxation of the femur is identified, surgical reconstruction of the acetabulum is recommended. The primary goals are to improve the coverage of the femoral head, and to prevent the development of or correct femoral subluxation and impingement. If these goals are achieved, the patient will have:

- a significant decrease in hip pain
- an improved range-of-motion of the hip
- an improvement in their gait pattern

The authors recommend the use of a modification of the triple osteotomy as described by Lipton and Bowen,[23] to address the acetabular deficiency. This technique acts as a closing wedge osteotomy to avoid undue stretch on the sciatic nerve. Other procedures to address the acetabular deficiency have been described.[11,24,25,26,27] The use of intraoperative monitoring of SSEPs and MEPs is highly recommended to help prevent irreversible nerve damage. Injuries to the peroneal nerve and the sciatic nerve have been reported.[11,27]

Surgical reconstruction of the femoral component should only be undertaken if the pelvic reconstruction procedure failed to reduce the femoral head within the hip joint and improve the coverage of the femoral head. A proximal varus derotation femoral osteotomy is then

performed to correct the increased anteversion and to redirect the femoral head into the acetabulum. The patient must be warned that there is a significant risk that the Trendelenberg gait may worsen following reconstruction of the femoral component of the hip. The new varus position of the proximal femur further weakens the magnitude of the abductor muscle forces at the hip joint. This combined with the already weakened hip abductor muscles due to the underlying peripheral neuropathy may worsen the Trendelenberg gait.

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Treatment Approaches for Charcot-Marie-Tooth Disease

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Introduction

Many advances have occurred in our understanding of the inherited neuropathies over the past 15 years. Unfortunately, these have not led to cures for any form of CMT. However, there are reasons to be optimistic that this will change. The dramatic progress in CMT-related research over the past 15 years is a result of the recent revolution in the field of molecular genetics. We have gone from a period in which no genetic cause of CMT was known to a time in which mutations in more than 30 different genes are known to cause neuropathies. Moreover, the exact disease causing mutation in most of these genes can be readily identified. We are now in the midst of a revolution in molecular biology. For the first time, scientists can evaluate cellular pathways of how mutated genes and their abnormal proteins cause CMT. Researchers have engineered “knockout mice”, in which the causal genes for many forms of CMT have been deleted. This enables us to determine the normal function of the gene in question. Similarly, other animal models have been and are being generated in which specific CMT causing mutations are introduced or “knocked in” to peripheral nerves. These animals not only serve as models to study disease mechanisms, but also as models in which we can evaluate treatments for patients with CMT. It is because of experiments in mouse and rat models of CMT1A that clinical trials of

medications for CMT1A are currently underway throughout the world. In the second part of the chapter we will review some of the promising therapeutic approaches for the treatment of CMT. However, more traditional therapies are also important for patients, and we will begin with a review of some of these treatment approaches.

Traditional Therapies

Patients, physicians, and scientists are understandably concerned with new and future treatments directed at curing CMT and other genetic neurodegenerative diseases. However, patients need treatment that is currently available. Unfortunately, an all too common experience is that patients with CMT are told that there is nothing that can be done for them. However, currently available therapies can help patients ambulate independently for many years, and plan for their families by knowing who is at risk to develop CMT. Therapy for CMT works best if it is provided in a multidisciplinary approach involving genetic counselling, neurology, physiatry, and in some cases, orthopedic and pulmonary support.

Genetic counseling

Competent genetic counseling is an extremely important element in the management of patients with inherited neuropathy. Counseling is based on the concept that a nondirective counseling approach is best for handling the complex issues that can arise when the diagnosis of an inherited condition is made. Patients with inherited conditions often seek further information regarding various decisions, including those concerning family planning. All options available to the patient, including prenatal testing, pre-implantation genetic diagnosis, sperm and egg donation, adoption, having children without any testing, and having no children can be explored. Patients are aided in making decisions that best fit with their beliefs, values, culture, and lifestyle. This approach can be difficult, especially when the clinician faces the inevitable question, “What would you do?” Although it is tempting to

answer this question with an opinion, it is important to keep in mind that the answer given may not be the best solution for a given patient. Nondirective counseling is based on the principle of autonomy and the belief that an individual is the person who knows what decisions are best for his or her life.

Physical therapy and exercise

Rehabilitation plays an essential role in preserving the quality of life of CMT patients, but data on which approaches should be standard is limited, due to insufficient scientific research. Weakness and muscle wasting, involving foot intrinsic muscles and leg muscles, are responsible for susceptibility to ankle sprains, poor balance, pain, clumsy gait, stepping gait and foot deformities, including *high arch foot* (pes cavus), *club foot* (pes equinovarus) and hammer toes. In the upper limbs, the impairment of intrinsic hand muscles often reduces dexterity, making activities such as buttoning a shirt or turning a key difficult. Therefore, a good rehabilitation program should increase muscle strength of those muscles that still function, improve mobility, prevent joint deformities, prevent falls, and improve hand function.

The role of exercise has only been addressed in a few studies involving CMT patients. In one study, a 12-week moderate resistance (30 percent of maximum isometric force) exercise program led to an improvement of muscular strength ranging from 4-20 percent, without any notable deleterious effects. The same group of patients underwent a 12-week high-resistance (training at the maximum weight a subject could lift 12 times) exercise program without further benefit (compared with the moderate resistance program) and with evidence of overwork weakness in some of the participants.[1,2] Overwork weakness is a potential concern in CMT, like in other neuromuscular diseases. In this respect, any exercise program that causes muscles to feel weaker within 30 minutes after exercise, or that causes excessive muscle soreness or severe muscle cramping, is discouraged. Certain low-impact aerobic exercise, such as walking

and swimming, can improve cardiovascular performance, increase muscle efficiency and help to control body weight. Thus, these types of exercise are useful with many patients with CMT. Gentle stretching may help fight muscle contractures.

Assistive devices

Depending on the level of muscle weakness and wasting, different devices are recommended. An initial foot drop with varus deformity and foot *inversion* (inward turning) can benefit from a lateral wedge to induce *eversion* (outward turning) and redistribute loading to a larger area of the foot. A more pronounced foot drop usually requires ankle-foot orthoses (AFOs), that should be custom-made and possibly of a lightweight material like polypropylene, carbon fiber resin or silicone, and fit intimately to provide good stability and prevent pressure sores. The older, traditional double metal upright AFOs built into the shoe may be too heavy. Most patients require a short course of physical therapy after the braces are made to help them use the braces effectively.

Medications and CMT

Medications to avoid

A common concern of CMT patients is whether particular medications might exacerbate their neuropathy. In general, medications that have clear neurotoxic affects, such as vincristine or cis platinum, should be avoided, if medically possible, in CMT patients because they would seem to have the potential to exacerbate the already existing neuropathy. There have been reports of severe weakness, similar to that seen in *Guillain-Barré Syndrome* (an inflammatory disorder of the peripheral nerves) in patients with CMT who were given vincristine. For other medications, the situation is less clear. The Charcot-Marie-Tooth Association (CMTA) publishes a list of medications that may exacerbate CMT on its web site, http://www.charcot-marie-tooth.org, and in its newsletter, *The CMTA Report*. The degree of risk varies with the individual medication, and in some cases, the risk may be

small compared to the medical need. Good judgment by the physician on the risk/benefit ratio of a given medication is a useful guide for the use of these medicines. The literature of medications exacerbating CMT has been recently reviewed in an article by Weimer.[3]

Pain management

Most patients with CMT do not develop neuropathic pain, which is characterized by burning or painful sensations in their feet or hands. Nevertheless, a minority of patients do experience these symptoms and the subject will be briefly addressed. Neuropathic pain can be quite difficult to treat and usually requires combination therapy in the opinion of this author. Recognizing that newer agents may become available, some of the more effective currently widespread agents are listed below.

Topical agents

Lidocaine and *prilocaine emulsion* are used topically for the treatment of painful neuropathies and are primarily effective on areas they are in direct contact with, such as the surface of the feet.

Tricyclic antidepressants

Amitriptyline, *nortriptyline* and *desipramine* are low cost, efficacious medications. Amitriptyline is the most frequently administered drug in this category. The dosage required for pain control may be significantly lower when compared with the doses normally used for anti-depressive purpose. Patients typically begin with lower doses, at bedtime, which are increased until they prove effective or induce toxicity. The main side effects include *orthostatic hypotension* (decrease in blood pressure upon standing), dry mouth, urinary retention, confusion and *somnolence* (an extreme form of drowsiness). They may also increase the risk of *cardiac arrhythmias* (abnormal heart rhythms).

Antiepileptic drugs

Gabapentin is an anticonvulsant drug that has been recently approved by the Food and Drug Administration (FDA) for the treatment of neuropathic pain. The mechanism of action of gabapentin is not clear, but it was designed as a precursor of the neurotransmitter gamma-aminobutyric acid (GABA) and was shown to increase the GABA content in brain synapses. It is also supposed to decrease the influx of calcium ions into neurons. The main side effects (dizziness, gait problems and somnolence) usually disappear after 10 days of treatment and may be minimized by slow increases in dosage. The only contraindication is *renal* (kidney) failure.

Lamotrigine acts through the inhibition of voltage-gated sodium-channels and has been demonstrated to be efficacious in the painful neuropathy associated with HIV infection. The usual dose is 200-500 milligrams (mg) per day, divided in two doses. The starting dose is 50 mg, which may be increased by 50 mg every two weeks. Increases must be made slowly to prevent hypersensitivity. Side effects include dizziness, *ataxia* (loss of muscle coordination) and nausea. If a skin rash appears, the drug should be discontinued because more serious allergic reactions may develop. Multi-organ failure or *blood dyscrasias* (a disorder that may lead to blood clots) are rare, but potential, serious side effects.

Carbamazepine is typically used to treat *trigeminal neuralgia* (a condition which produces pain in the trigeminal nerve in the face), but it has also been used for years to treat other painful neuropathies. The dosage is 200-400 mg, divided in two to three doses daily. The most common side effects of carbamazepine are dizziness, ataxia and *dyspepsia* (upset stomach), all of which may be prevented by slow increments. A complete blood count should be carefully monitored to detect blood dyscrasias, including *agranulocytosis* (a drop in white blood cells) and *aplastic anemia* (a disease in which the bone marrow stop producing blood cells), which may occur as a result of an individual's particular hypersensitivity.

Pregabalin and *duloxetine* are two medications that are beginning to receive widespread use in the treatment of painful neuropathies. Pregabalin, like several of the medications listed above, was originally developed as an antiepileptic agent and was found to be effective in treating *nociceptive pain* (pain associated with a painful stimulus). Duloxetine is another of the antidepressant agents that also appear to reduce neuropathic pain. Whether these medications prove more effective than those discussed above is unknown at this time.

A review of many of these agents in the treatment of peripheral neuropathies is provided in a paper by Grandis and Shy.[4]

Although beyond the scope of this review, many CMT patients develop chronic, aching pain in joints as a result of arthritic damage exacerbated by their CMT. These pains are typically treated with medications, such as non-steroidal anti-inflammatory drugs, which are used to treat chronic osteoarthritis pain in patients that do not have CMT.

Biologically Based Treatment Strategies

The detection of CMT-causing mutations in many different genes and proteins has identified a number of intracellular pathways that contribute to causing neuropathy and the resulting disability. Manipulation of these pathways will be at the heart of future therapeutic strategies to treat CMT. Several are discussed below.

Gene dosage and regulating myelination: Therapy for CMT1A

The most common form of CMT, CMT1A, is caused by a duplication of a particular segment of chromosome 17 in the region carrying the *PMP22* gene, which encodes the protein PMP22. It is the additional PMP22 protein that causes the neuropathy, as confirmed by the development of a similar peripheral neuropathy in genetically

engineered mice and rats with equivalent over-expression of the protein. In contrast, when the *PMP22* gene is deleted, instead of duplicated, patients develop a different disorder, Hereditary Neuropathy with Liability to Pressure Palsies (HNPP), which affects patients differently than does CMT1A. Patients with HNPP develop temporary episodes of regional weakness or loss of sensation, whereas patients with CMT1A primarily develop slowly progressive weakness and sensory loss of their feet and hands. Taken together, CMT1A and HNPP demonstrate the importance of PMP22 protein dosage in preventing or causing neuropathy. Scientists, therefore, are beginning to develop treatment strategies for CMT1A that are based on regulating PMP22 protein dosage, several examples of which are discussed below.

A progesterone antagonist improves neuropathy in CMT1A rats

During the process known as transcription, genes are transcribed into messenger RNAs (mRNA), which are subsequently translated into proteins during what is known as *translation*. A German group noted that the hormone progesterone increased the transcription levels of *PMP22* and *MPZ* mRNA in cultures of Schwann cells, the cells that make myelin. They reasoned that by manipulating the amount of progesterone, one might be able to manipulate the levels or dosage of PMP22 protein as a treatment strategy for CMT1A, which results from too much PMP22 mRNA and protein. These same investigators had previously developed a rat model of CMT1A. They decided to treat these animals either with progesterone or an antagonist (a substance that prevents the activation of a receptor) to progesterone, onapristone, in order to further raise or lower the PMP22 protein levels of the rats.

As predicted, feeding the rats progesterone made their neuropathy worse, as the already elevated PMP22 levels were raised further. However, onapristone lowered PMP22 levels and improved the neuropathy. Taken together, these experiments have provided a proof of principle that the progesterone receptor of myelin-forming

Schwann cells is a promising pharmacological target for therapy of CMT-1A.[5] Unfortunately, onapristone has been shown to be toxic to humans, so it will probably not be used in clinical trials. However, current research is underway to develop a less toxic progesterone antagonist that can be used in clinical trials of CMT1A.

Ascorbic acid and CMT1A

A group of French scientists has genetically engineered a line of mice to have the same mutation in their DNA that causes CMT1A in people. As expected, the mice develop a peripheral neuropathy with many of the features of CMT1A. These same scientists then elected to treat the mice with large doses of *ascorbic acid* (vitamin C). This decision was based on previous studies in tissue cultures in which Schwann cells will make myelin around cultured nerve cells if ascorbic acid is added to the tissue culture media. Preliminary results demonstrated improvement in the treated mice. They were able to balance on a rotating rod, which untreated mice could not do. The treated mice also had more normal *PMP22* mRNA levels and larger numbers of myelinated fibers in their nerves.[6] Because of these encouraging results, clinical trials of ascorbic acid in the treatment of CMT1A are now beginning on several continents.

Treatments with progesterone antagonists or ascorbic acid are not specific for PMP22, because neither has been shown to particularly target expression of a single myelin gene, for example. Rather, both therapies appear directed towards regulating the overall program of myelination. Whether progesterone antagonists or ascorbic acid would be candidates for treating additional forms of CMT1 is not currently known and has not yet been investigated in animal models.

Trophic factors and CMT

Trophic factors (growth factors) are molecules produced in the body that promote growth of nerve cells and their processes. Three families of trophic factors have been used in recent years to treat models of neurodegenerative diseases, including CMT. The first of

these is the Neurotrophin family, which, in mammals, consists of nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin 3 (NT3), and neurotrophin 4/5 (NT4/5). Neurotrophins act by binding to and activating specific receptors, most of which are what are known as protein tyrosine kinase (Trk) receptors. When activated, these Trk receptors activate signaling pathways within the target cell that alter the cell's behavior. All the neurotrophins can also bind to what is called the *low affinity p75 receptor,* which can signal target cells independently of the Trks.

The second family of trophic factors being used to treat neurodegenerative diseases is the glial cell derived neurotrophic factor (GDNF). GDNF family members include GDNF itself, as well as molecules named neurturin, artemin, and persephin. GDNF family members bind to other proteins and ultimately to a common signal transducing subunit, c-ret, which is also a protein kinase receptor that causes biological changes in the target cell.

The third family is the ciliary neurotrophic factor family (CNTF) family of cytokines that includes CNTF, leukaemia inhibitory factor (LIF), cardiotrophin 1 (CT-1), cardiotrophin-like cytokine (CLC), and the interleukens 6 (IK-6) and 11 (IL-11). All members share a common set of receptors, which have the membrane protein, gp130, as a common signal transducing subunit.

Enthusiasm for the use of trophic factors to treat CMT and other degenerative disorders results from the known ability of these compounds to make nerve cells grow. However, these effects often only occur at certain times of nerve development and in very specific environments. Therefore, the medicinal use of these molecules is not as simple as merely introducing a trophic factor into a nerve and expecting the factor to reverse a patient's peripheral neuropathy. Many of the trophic factors cited above have been shown to rescue or ameliorate some animal or tissue culture models of nerve damage. However, as yet no patient with nerve disease has had their

neuropathy reversed by the administration of a trophic factor, despite multiple clinical attempts. Most of the trophic factors cited above are already expressed in Schwann cells or neurons, and their levels are often already increased in these cells following nerve injury. Whether further increases will prove more effective than the bodies' own elevated levels is not known. This topic is reviewed in more detail in the review by Massicotte and Scherer.[7]

Neurotrophin 3 treatment of CMT1A

One recent report has suggested that NT-3 may prove helpful in treating the sensory loss found in CMT1A, although these results need to be interpreted with caution because they were only performed in four patients and four controls. In these patients, sural nerve biopsies were taken and evaluated after the patient had been treated for six months with injections of NT-3. The NT-3 appeared to promote nerve regeneration in these sensory nerves. Clinically, treated patients could detect slight improvements in their ability to detect pinprick and vibratory sensations in their toes.[8] While these results need to be interpreted with caution, given the small sample size and short duration period, they suggest that NT3 may prove beneficial in treating sensory loss in CMT1A and clinical trials investigating this possibility are currently being considered.

Gene Therapy

Gene therapy can be defined as a strategy to transfer biologically relevant genetic material into affected cells in the body to treat disease. While this may seem to be a futuristic dream, gene therapy studies have been extensively carried out for more than a decade to develop treatments for neurodegenerative diseases. In general, approaches in gene therapy have followed two paths. The first is the development of delivery vectors or systems to target therapeutic genes and their products to neurons or Schwann cells. The second approach has been to develop genetically engineered cargoes to be carried to the cells by the vectors.

Gene therapy delivery systems

Most gene therapy delivery systems utilize portions of viruses that have been modified so they can't cause disease but will still carry the therapeutic gene to the cells that the virus usually infects. A detailed discussion of these different viral vectors is beyond the scope of this chapter. However, the topic is reviewed in more detail in a recent review published in *NeuroMolecular Medicine.*[9]

Stem cells

Embryonic stem cells that could potentially develop into Schwann cells or neurons have generated a great deal of excitement among families with CMT, as well with investigators in CMT research. However, there are formidable challenges to the use of stem cells in the inherited neuropathies. It is a difficult challenge for stem cells to differentiate into neurons and then generate axons that would need to travel down limbs more than a meter prior to reaching their appropriate neuromuscular junction or sensory endings. Similarly, it will be difficult for stem cells to differentiate into Schwann cells and then contact axons because many mutated Schwann cells will still be *ensheathing* (covering) axons in demyelinating forms of CMT, even if they are not generating a normal myelin sheath. However, another potential use of stem cells might be as a source of trophic support for inherited neuropathies. Stem cells could be engineered to differentiate relevant trophic factors or other molecules and then be transplanted into the peripheral nervous system. For example, a clone of neural stem cells genetically modified with a retroviral vector continued to produce NT-3 for at least two months after being transplanted into rat spinal cord. Subsequent injections of the NT-3 expressing stem cells partially prevented the loss of neurons in Clarke's nucleus (a section of grey matter in the spinal cord) following transection of their axons.

Gene therapy cargo strategies

Gene replacement

Mutant genes that cause neuropathy by a simple loss of their normal function of the normal gene are among the most promising targets for gene therapy. In this situation, the treatment should require simply replacing the missing gene product rather than the repair of an abnormal new function introduced into the cell by the mutant protein. Candidate CMT types for "simple" gene replacement include the autosomal recessive forms of CMT. As with other recessive diseases, most CMT4 cases are thought to result from loss of function of the normal gene. In addition, gene replacement would appear an appropriate strategy for some dominant forms of CMT that appear to result from a loss of normal function. One obvious candidate is HNPP, caused by the deletion of one of the two *PMP22* alleles. Additional targets for gene replacement are nonsense mutations that cause premature termination of various mutant proteins, and also may result in what is termed "nonsense mediated decay" in which truncated mRNAs are degraded. Finally, CMTX1 may prove susceptible to simple gene replacement. Despite the fact that there are more than 260 distinct *GJB1* mutations that cause CMTX1, many of the phenotypes appear similar to those expressed in families that have the entire *GJB1* gene deleted, suggesting that their neuropathies are caused by simple loss of function.

Gene dosage reduction

CMT1A, the most common form of CMT, is caused by an increase, rather than a decrease, of PMP22. As a result, a gene therapy approach to CMT1A needs to reduce the amount of *PMP22* mRNA and protein. An emerging strategy for this is the field of posttranscriptional gene silencing. Small double-stranded RNAs (dsRNA), of approximately 21 nucleotides, are used in plants and animals to degrade mRNA in a sequence-specific manner. Similar small inhibitory RNAs (siRNAs) can be genetically engineered to reduce the expression of target mRNAs, such as *PMP22* in patients with CMT1A. Catalytic RNA molecules, known as ribozymes and

antisense oligonucleotides, also have the potential to down regulate levels of mRNAs in a sequence specific manner. In fact, an antisense oligonucleotide to *PMP22* mRNA has been combined with an inducible promoter to generate transgenic mice in which *PMP22* mRNA levels, and peripheral neuropathy, can be modulated by feeding the animals tetracycline. In theory, because all of these approaches involve sequence specificity, they could be used to reduce expression of genes containing missense mutations causing gain of function abnormalities.

Perspective

At the time of this review, no genetically affected Schwann cell or neuron has been cured of disease by gene therapy, although there have been some successes with gene therapy in animal models and in tissue culture studies. Nevertheless, it seems premature to conclude that the concept of gene therapy is a failure. Gene therapy is still a relatively new field. New vector systems continue to be developed. New methods of introducing gene therapy vectors are continuously emerging. For example, intravascular administration of viral vectors in the presence of vasodilators appears capable of transducing many more cells than was previously possible. Moreover, it is difficult to imagine future cures for genetic neurodegenerative disorders such as CMT that will not require some form of gene therapy.

Future Molecular Targets

There are presently enough different genes causing CMT that together they can be thought of as a living microarray of genes that are necessary for the normal functioning of the Schwann cells and peripheral nerve neurons. The more than 30 proteins encoded by these genes can also provide clues into cellular pathways that contribute to the pathogenesis of CMT. Some of these cellular pathways are shown in Figure 1 and summarized in Table 1, both of which have been modified from recent reviews.[10]

Figure 1. Cellular Pathways

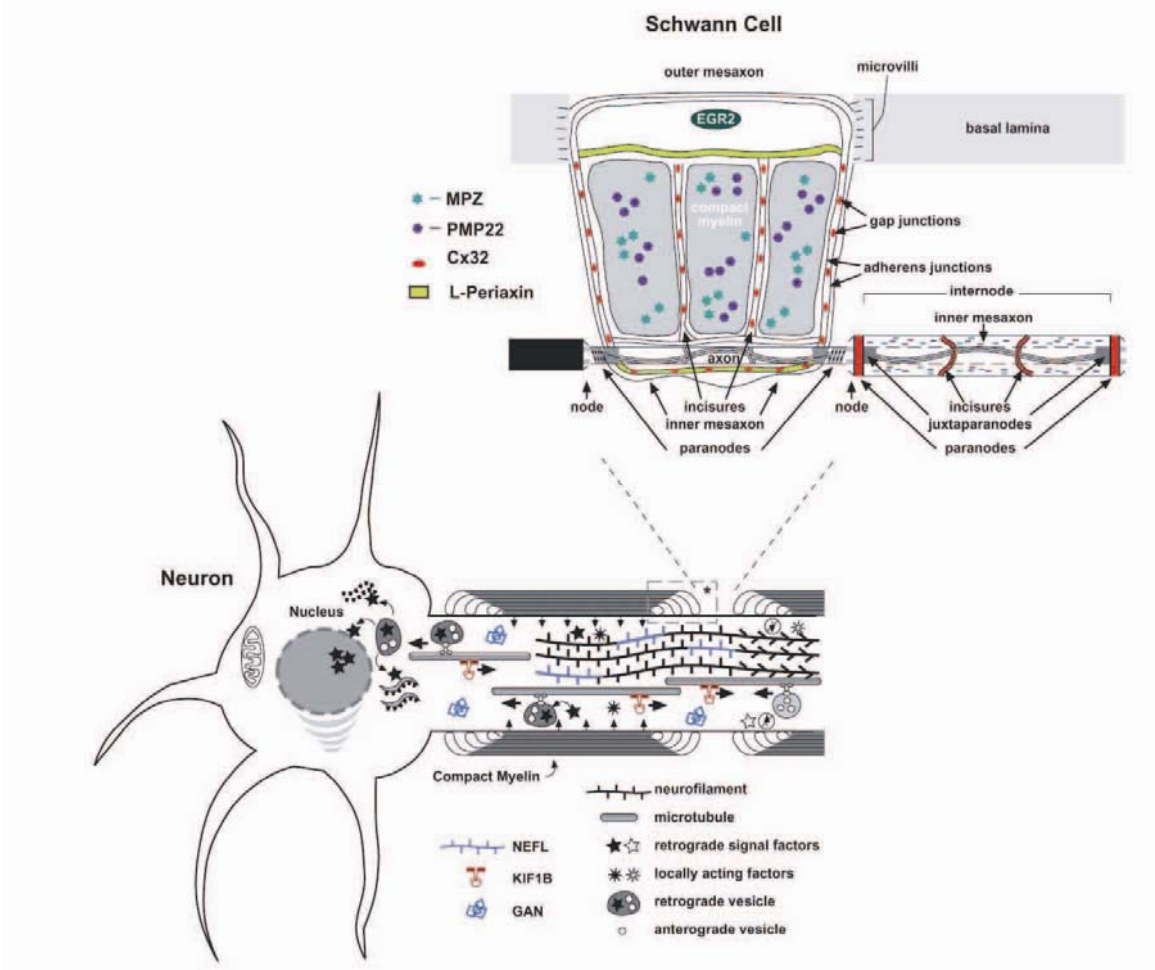

Table 1. Future Molecular Targets

Cellular process	CMT type	Relevant gene
Axonal transport	CMT2A	*MFN2*
	CMT6	*MFN2*
	Giant axonal neuropathy	*Dynactin*
	SPG10	*KIF5A*
Mitochondrial function	CMT2A	*MFN2*
	CMT6	*MFN2*
	Familial ALS	*SOD 1*
Membrane fusion/fission	CMT1C	*Litaf/Simple*
	DI-CMT	*DNM2*
	SMA/ALS	*VAPB*
Protein misfolding	CMT1A	*PMP22*
	CMT1B	*MPZ*
DNA/RNA processing	CMT2D/HMNV	*GARS*
	DI-CMTC	*YARS*
	ALS4	*SETX*
	SMARDI	*IGHMB2*
	SMA	*SMN*
SC-axonal interactions	Demyelinating CMT	Multiple genes

Disruption of axonal transport

Neurons transport proteins, cytoskeletal elements, synaptic vesicle precursors, mitochondria, and other organelles along axons that are sometimes more than a meter in length. Orthograde transport, from the cell body down the axon, is facilitated by molecular motors known as kinesins, a gene family whose members carry specific cargoes along tracks of microtubules down the axon. "Fast" retrograde transport in motor axons carries organelles and material in the opposite direction. This retrograde transport is carried out by dynein-dynactin complexes that serve as motors to return materials to the cell body from nerve terminals, for restoration and reuse. Disruption in both orthograde and retrograde transport probably causes some forms of CMT as well as other neurodegenerative

disorders. Kinesin *KIF5A* mutations cause a dominantly inherited spastic *paraparesis* (weakness of the lower extremities), possibly by disrupting microtubule-dependent axonal transport of neurofilament. Mutations in the *dynactin* gene cause a chronic motor neuron disease. In this latter disorder, a single base-pair change, resulting in an amino acid substitution, is predicted to distort the folding of the dynactin domain responsible for binding to the microtubules. This domain is necessary for retrograde transport. In another disorder, recessive mutations in the *gigaxonin* gene cause giant axonal neuropathy. Gigaxonin binds to microtubule associated protein 1B (MAP1B) to enhance microtubule stability. Presumably, a disruption in microtubule stability in giant axonal neuropathy contributes to the pathogenesis of this unusual disorder.

Finally, axonal transport of mitochondria is probably disrupted in CMT2A, the most common form of CMT2. CMT2A is caused by mutations in the nuclear encoded mitochondrial gene *mitofusin 2* (*MFN2),* and will be cited again under the heading of mitochondrial disorders. Mitochondria need to fuse into chains before being transported by kinesin *KIF1B*. Several *MFN2* mutations appear to prevent mitochondrial fusion. Taken together, these results suggest that disrupted axonal transport of mitochondria may contribute to the pathogenesis of CMT2A. It has been proposed that disruptions in axonal transport are responsible for length-dependent axonal degeneration in many neurodegenerative disorders. Repairing axonal transport is an attractive therapeutic approach to treating many forms of CMT.

Mitochondrial function in CMT

Mitochondrial abnormalities have been found in a number of neurodegenerative disorders, including Alzheimer disease, Parkinson disease, and spastic paraplegia. They have also been identified in an increasing number of inherited neuropathies. MFN2, the cause of CMT2A, is a *dynamin*-like GTPase that spans the outer mitochondrial membrane where it helps mediate mitochondrial fusion. Mitochondria

exist in a dynamic state, alternating between fusion and fission. As noted above, mitochondria need to fuse in order to be carried by kinesins in orthograde axonal transport. In addition, *MFN2* mutations are likely to disrupt normal mitochondrial functions, such as supplying energy to the cell or participating in *apoptosis* (programmed cell death) pathways.

Mutations in the putative glutathione transferase protein GDAP1 cause CMT4A. GDAP1, also encoded in the nucleus, is predominantly expressed in neurons where it associates with mitochondria. Mammalian glutathione transferase families are involved in the inactivation of endogenous hydroperoxides formed as secondary metabolites during oxidative stress. GDAP1 has been found to co-localize with mitochondria in a series of *in vitro* transfection (the introduction of foreign DNA) assays. Its function in mitochondria is, at present, unknown.

Mutations in *superoxide dismutase* 1 (*SOD1*) cause approximately 20 percent of cases of familial amyotrophic lateral sclerosis (FALS). *SOD1* is localized to mitochondrial membranes and it has been proposed that alterations in mitochondrial function are involved in the pathogenesis of FALS. Recently, it has been found that small heat shock proteins such as HSP27, the cause of CMT2F and a form of distal hereditary motor *neuronopathy* (dysfunction due to damage to neurons of the peripheral nervous system), block the uptake of mutant *SOD1* into mitochondria, although not that of wild type *SOD1*. It is hypothesized that this binding would make heat shock proteins unavailable for their apoptotic function that would ultimately lead to motor neuron death.

Taken together these CMT models suggest that manipulating mitochondrial function is an area of potential therapeutic research into at least some forms of CMT.

Membrane fusion, fission, and protein transport

Fusion and fission are important cellular processes in other areas of the cell besides mitochondria. In addition to *MFN2*, several forms of CMT and related disorders appear to be caused by abnormalities in the fusion and fission of other cellular membranes. The GTPase *dynamin 2* (*DNM2*) mutations cause dominant intermediate CMT (DI-CMT). The role of *DNM2* appears to be in aiding the separation of newly formed endosomes from the cell membrane. Additionally, the vesicle-associated protein B (VAPB) participates in membrane fusion and has recently been shown to cause ALS in several Brazilian families. VAPB contains a v-SNARE domain. SNARE refers to soluble NSF-attachment protein receptor proteins. Membrane proteins from vesicles (v-SNARES) and proteins from target membranes (t-SNARES) govern the specificity of vesicle targeting and docking through mutual recognition. However, members of the vesicle-associated protein family also associate with microtubules and function in membrane transport.

Mutations in the putative protein degradation protein LITAF/SIMPLE cause the demyelinating autosomal dominant disorder CMT1C. Initial patients with CMT1C have had phenotypes that strongly resemble those with CMT1A. Although the precise function of SIMPLE is unknown, its murine orthologue interacts with Nedd4, an E3 ubiquiton ligase. Mono-ubiquitination of plasma proteins by Nedd4 family members serve as internalization signals that are recognized by protein TSG101 that facilitate the sorting of membrane proteins to the lysosome for degradation. Although SIMPLE is expressed in many cell types when mutated, it seems to cause only a demyelinating neuropathy. This suggests that the disease specificity may come from impaired targeted degradation of specific Schwann cell proteins such as PMP22.

Protein misfolding and ER retention

PMP22 missense mutations Leu16Pro and Leu147Arg cause a demyelinating neuropathy in humans and the naturally occurring

demyelinating trembler J (Tr^J) and trembler (Tr) mouse mutants. Because both of these mutations are more severe in humans than HNPP (also more severe than CMT1A caused by *PMP22* duplication) they are likely to cause disability by causing an abnormal gain of function by the mutant *PMP22*, rather than by a simple loss of *PMP22* function. When epitope-tagged Tr, Tr^J and wild type *PMP22* were microinjected into sciatic nerves of rats and analyzed by immunohistochemistry (the use of antibodies or antisera to study cells or tissues), wild type *PMPP22* was transported to compact myelin, but both Tr and Tr^J *PMP22* were retained in a cytoplasmic compartment that co-localized with the endoplasmic reticulum (ER). Other studies have also shown that mutant Tr and Tr^J proteins aggregate abnormally in transfected cells. In fact, structures similar to aggresome (a region of the cell where protein aggregates collect) structures have been identified in sciatic nerves of Tr^J mice, surrounded by chaperones and lysosomes, suggesting that abnormalities in intracellular degradation of mutant *PMP22* contributed to the pathogenesis of the neuropathy.

More recent studies have shown that there are abnormalities of proteosome function resulting in the accumulation of ubiquitinated substrates in the Tr^J model. Recent cell-based studies showed that mutant *MPZ* could accumulate in the endoplasmic reticulum and induce apoptosis. This aggregation-induced apoptosis was abrogated by pretreatment with *curcumin* (a pigment of the spice turmeric). Whether curcumin will have similar effects in whole animal studies remains to be determined. Transfection studies have also demonstrated that other *PMP22* and *MPZ* mutations result in mutant proteins being retained in intracellular compartments.[11] Whether these other mutations also disrupt proteosome activity or cause abnormal gain of function by other mechanisms, such as activating the unfolded protein response (UPR), are areas of active investigation that may lead to future treatments.

Ribonucleic acid processing

Extensive RNA processing occurs following transcription prior to the formation of proteins in the process of translation. Nascent RNA transcripts undergo splicing, add a cap to their 5' end and a polyalanine tail to their 3' end prior to leaving the nucleus for the ribosome. Transfer RNAs specifically add their cognate amino acid to the developing protein on the ribosome. One might expect that abnormalities in all of these processes would seriously disrupt all cells, not just those of the peripheral nervous system. Interestingly, mutations in a number of genes involved in these processes appear to cause primarily CMT or a similar disorder. GARS is a glycyl-tRNA transferase that is responsible for placing a glycine on the appropriate tRNA in both the cytoplasm and mitochondria. This is an essential process in all cells. However, missense mutations in GARS appear to cause only CMT2D and distal hereditary motor neuropathy (dHMN) type V.

Senataxin contains a DNA/RNA helicase that causes ALS4 and dHMN. It has been proposed to participate in DNA repair. Mutations in *senataxin* have also caused ataxia-ocular apraxia type 2. *Senataxin* also is homologous to immunoglobulin mu binding protein 2 (IGHMB2), another DNA/RNA helicase that has a putative role in transcriptional regulation and splicing. Mutations in IGHMB2 cause a variant of infantile SMA called SMARD1.

Werdnig-Hoffman, Kugelberg-Welander, and the other classic forms (I-IV) are caused by mutations in the survival motor neuron (SMN) protein, which is part of a complex of proteins that participates in the assembly of spliceosomal *small nuclear ribonucleoproteins* (snRNPs) The SMN complex binds to specific sequences in the snRNAs and facilitates snRNP assembly.

Schwann cell-axonal interactions

Schwann cell-axonal interactions are necessary for normal axonal function and are often disrupted in demyelinating inherited

neuropathies, causing significant changes in axonal physiology. Consequences of these disruptions include changes in the *phosphorylation* (the chemical addition of a phosphate group to a protein or another compound) status and packing density of neurofilaments and abnormal axonal transport. Ultimately, axonal degeneration occurs, which may contribute more to disability than the initial demyelination. Therefore, strategies directed towards preserving Schwann cell interactions may play an important role in future therapies for the demyelinating forms of CMT. Currently these strategies are focusing in three areas, one of which is to provide trophic factor support that has been previously discussed.

The second strategy is based on the hypothesis that demyelination places increased energy demands on the neuron to generate action potentials and salutatory conduction velocity. Thinning or absence of myelin reduces its ability to maintain a charge separation that results in a leaking of capacitance. Thinning of the axon, perhaps from decreased neurofilament phosphorylation, leads to increased electrical resistance along the axon. Taken together, these factors make it more difficult for depolarization to occur at *nodes of Ranvier* (regular intervals along peripheral axons where the myelin sheath is interrupted; the points between which nerve impulses jump, rather than pass, along the fiber). This “impedance mismatch” can even lead to conduction block at individual nodes of Ranvier. It also places increased energy demands on the neuron to propagate action potentials by salutatory conduction. Voltage-gated potassium channels (Kv1.1 and Kv1.2) are exposed on the *axolemma* (the membrane of a neuron’s axon) as a consequence of paranodal retraction, a common early feature of demyelination. As a result, potassium ions can leak out of the axon, down their concentration gradient, also making it more difficult for depolarization to occur at the node of Ranvier.[12]

This has led investigators to consider the use of potassium channel blockers to treat demyelinating neuropathies, including CMT1.

Preliminary studies with 3,4 diaminopyridine did not demonstrate significant improvement in a population of CMT patients, most of whom had CMT1. However, more specific potassium channel blockers are becoming available including agents that are capable of blocking the channels from inside the axolemma. These may have better access to the channels than agents such as 4-aminopyridine that bind to potassium channels at their extracellular surface. Sodium channel blocking, in order to protect the neuron, has also been proposed as a treatment in chronic demyelinating neuropathies. This approach would not prevent conduction block or promote salutatory conduction. However, it would theoretically protect the neuron from "overwork" because it would inhibit the ability of the sodium channels to depolarize the axon in the generation of the action potential.

The third strategy to improve Schwann cell-axonal interactions is to identify and manipulate specific signaling pathways between the Schwann cell and the axon. Nave and his colleagues[13] have recently demonstrated that peripheral nervous system myelin thickness is regulated by neuregulin 1 (Nrg1) signaling from axons. Nrg1 is the founding member of the Neuregulin family that belongs to the epidermal growth factor (EGF) superfamily. Nrg1, like other members of the EGF superfamily, binds to members of the ErbB receptor tyrosine kinase family. ErbB2 and ErbB3 are neuregulin receptors expressed in Schwann cells. Ligand binding to the receptors results in their dimerization and activation of signal transduction pathways, including PI3-K and *ras*lMAP kinase. While Nrg1 mutations have not been shown to cause CMT, manipulations of this pathway could theoretically be used to manipulate myelin thickness in the future as a treatment modality, particularly because, as the authors point out, the Nrg1 C-terminal domain can be cleaved to become a signaling molecule itself.

Possible sites for other specific signaling interactions between Schwann cells and axons include the adaxonal internode, and the paranodal region of the myelinating Schwann cell. The axolemma is

divided into a series of polarized domains in which particular molecules are expressed in specific areas such as the node of Ranvier, paranode, juxtaparanode, and internode. A similar organization occurs in regions of adaxonal myelin that appose these domains. Further defining molecular pathways through which the adaxonal myelin and underlying axolemma interact may provide therapeutic targets to prevent or minimize axonal degeneration in demyelinating neuropathies. However, no other specific signaling pathways between Schwann cells and axons that might prevent axonal degeneration have yet been identified.

These topics are all discussed in detail in the reviews by Zuchner and Vance[14], Massicotte and Scherer, and Shy.

Prenatal Genetic Diagnosis

Couples at risk for transmitting genetic disorders are increasingly interested in research advances that can ensure that their children will not be born with or develop significant phenotypic abnormalities. Past options for these couples have included deciding to remain childless, considering gamate donation or adoption, or having a prenatal diagnosis followed by termination in case of an affected fetus.[15] There are obviously personal ethical considerations involved in these and related issues designed to ensure that a developing fetus is not born with a particular disease. However, recent advances in pre-implantation genetic diagnosis (PGD) have given parents an additional option to reduce the likelihood of transmitting inherited diseases, such as CMT.

Prenatal genetic diagnosis uses standard techniques of *in vitro* fertilization (IGF) and *in vitro* embryo culture. The fertilized egg typically undergoes reductive cell division and reaches the eight-cell stage at around three days post-fertilization. By the time the embryo reaches the blastocyst stage, the discrete clump of cells destined to become the fetus is identifiable. Prenatal genetic diagnosis requires

the biopsy of either the oocyte or this developing embryo. The biopsied material is tested for the genetic disorder, usually by a form of polymerase chain reaction (PCR) or fluorescence *in situ* hybridization (FISH), and unaffected embryos are transferred to the uterus. As an alternative, first and second polar bodies are biopsied and results used to infer the genetic diagnosis, though these results may be less certain. The most widely used approach is to biopsy single blastomeres from embryos on day three.

Prenatal genetic diagnosis has been used in CMT, although its use is not widespread and there is only a little data available to judge its effectiveness. One recent report documents the effective use of prenatal genetic diagnosis in five couples with CMT1A, caused by the duplication on chromosome 17. Fluorescence-based PCR tests were used to ensure that healthy, unaffected embryos were transferred to the uterus. In theory, a multiplex PCR-based approach should prove capable for detecting missense mutations causing other forms of CMT, although data supporting the effectiveness of such studies in CMT is not yet available.

Conclusions

To summarize, nothing could be farther from the truth than to state that there is nothing that can be done for patients with inherited neuropathies. In most cases, there are already a great number of treatments available, including orthotics, physiatry assistance, and orthopedic surgery that can each markedly improve a patient's quality of life. Genetic diagnosis and counseling based on rigorous genetic testing make a precise diagnosis and family planning possible to a degree that was impossible until just a few years ago. Therapeutic trials based on a rational understanding of the various neuropathies are now being undertaken. Gene therapy studies are beginning in animal models of CMT. Perhaps in the next generation we can begin to think of CMT as curable, rather than simply a treatable collection of peripheral neuropathies.

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Physical Exercise Programs for Patients with CMT

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Those who are affected with Charcot-Marie-Tooth disease (CMT) have received mixed messages concerning whether or not to exercise. For many years, physicians advised patients with CMT that exercise could cause their disease to progress more rapidly or that it might cause muscle or joint injuries. Other questions remain unanswered. In addition to concerns regarding safety, questions remain as to whether exercise could instead slow the disease progression, which other benefits might result from exercise, and which type of exercise would be most beneficial. Even now these questions are not answered fully, although some medical evidence provides answers to some questions about exercise and CMT. Some studies are underway that might provide answers to people with any type of neuromuscular disease.

When one considers whether exercise is safe for patients with CMT, it is helpful to review the potential benefits from exercise. Physical

exercise can increase the ability to perform all activities, including activities of daily living, by improving strength of movement and improving utilization of oxygen. CMT does not affect the muscle function directly; therefore, exercising would not be hindered by poor recovery of the muscle from exercise. There is no indication that CMT changes the proteins in the muscle that work to recover from any injury to muscle, exercise stress, or buildup of exercise byproducts in the muscle. In addition, people with CMT have the same general health-risk factors as anyone who has a sedentary, nonexercising lifestyle. This means that the same increased risks exist for diabetes, heart disease, high blood pressure, or stroke that result from being physically inactive.

With that in mind, one might ask what might hinder or keep someone with CMT from exercising. If the patient has known heart problems, shortness of breath, hypertension under poor control, or diabetes under poor control, exercising could be dangerous and should not be started without evaluation by the primary care doctor. If the patient has orthopedic limitations, such as the need for assistive devices, or marked reduction in strength (<15 percent of healthy adult strength), exercise may still be helpful and possible. However, accommodations or adaptations might have to be made to the design of an exercise program in order for the patient to avoid injury or to enhance the benefit from the exercise.

Only a few studies in the scientific literature have looked at the effect of resistance exercise on people with CMT. Most of these have been studies that grouped people with multiple neuromuscular diseases together into one single study to try to get an idea of a general effect, as well as possibly a specific exercise effect, positive or negative, in each disease. One study (Aitkins et al., 1993) looked at 27 people (eight of whom had CMT) using low-to-moderate strength training for upper and lower body, and all the subjects showed improved strength after 12 weeks. A higher intensity program (Kilmer et al., 1994) studied 10 people with neuromuscular diseases (two of whom had

CMT) over a period of 12 weeks, and results showed some negative effects on strength. Another study (Lindeman et al., 1995) employed a 24-week home-based resistance training exercise program for people with CMT or with myotonic dystrophy. The people with myotonic dystrophy did not show any improvement in strength, but those with CMT acquired greater strength and believed that they were able to perform better in many of their activities of daily living. Results were based on answers to a questionnaire. Blood levels of muscle enzymes that indicate muscle breakdown or injury did not increase, which implies that no excessive muscle damage resulted from the exercise.

A study comparing creatine supplementation (Chetlin et al., 2004*a*) versus placebo in a 12-week resistance-training exercise program enrolled 20 people with CMT. Although there was no difference between the two groups who took creatine versus placebo, all subjects had improved strength, improved ability to perform activities of daily living, improved lean body mass, and enlargement or hypertrophy of muscle fibers (determined by muscle biopsy) after 12 weeks of strength training.

Based on this information, there is reason to believe that exercise will improve strength and function in people with CMT, especially if done in moderation. But are there reasons for people with CMT to exercise other than these modest improvements in function and strength? People with CMT get the same overall health gains from exercise that people who do not have CMT gain, which includes improvement of cardiac function, reduction of risk factors for heart disease and diabetes, and reduction in body fat percentage. Based on the results of one study, (Chetlin et al., 2004*b*) people with CMT may be at higher risk for heart disease, based on their high body fat percentage, obesity, and poor exercise tolerance. This study also showed that these CMT subjects had an incidence of type 2 diabetes three-and-one-half times greater than that in the general population.

Table 1. Suggested Directions for Weight Assignment Based Upon ADL Performance *(Chetlin et al., 2004b)*.

Step	Recommended Procedure
One	Using a stopwatch, take two timed measurements of chair-rise and supine-rise performance. Instruct patients to start on "Go" command. Start timing at first sign of movement. For the chair-rise, instruct patients to sit with back against the chair, feet flat on the ground and spread at a comfortable distance, and arms crossed in front of the body. Time stops when patient is in stable standing position. For supine-rise, have patients lie flat on exam table with arms at sides. Time stops when patient achieves seated position with feet on floor. Patients are encouraged to use both upper and lower body to achieve the seated finish position.
Two	Take the faster of the two timed measurements for the purpose of determining starting weight assignment.
Three	On Table 2, locate the appropriate tertile for each ADL. If the patient's performance falls to the slower end of the range, use the lighter end of the recommended starting weight for the prescribed exercise mode. If the patient's performance is toward the faster end of the range, choose a weight in the heavier end of the range. If patients cannot complete all the reps and sets with the selected weights, have them lower the resistance 1-2 pounds until they reach a weight to complete all the reps and sets during a single training session.
Four	Have the patient increase the number of repetitions for each exercise on a weekly basis without changing the assigned weight: Week 1: 4 repetitions x 3 sets Week 2: 6 repetitions x 3 sets Week 3: 8 repetitions x 3 sets Week 4: 10 repetitions x 3 sets
Five	Re-evaluate the patient's ADL times after 3-4 weeks. Refer to Step Three in this table to assign new weight to be lifted.
Six	Advise patients to either maintain their strength gains by continuing to exercise at the level they attained at 12 weeks, or progress conservatively. For those patients who want to progress, increase the weight one to-two pounds for the upper body and two-to-four pounds for the lower body, provided they can complete all the repetitions and all the sets without severe soreness or fatigue.

Table 2. Resistance training model for CMT patients based upon ADL performance *(Chetlin et al., 2004b*).

	Chair-rise performance by tertile (seconds)						Supine-rise performance by tertile (seconds)					
	Low 1/3		Mid 1/3		High 1/3		Low 1/3		Mid 1/3		High 1/3	
4-week Training **Phase I**	0.89-1.10s		1.11-1.41s		1.42-2.02s		1.34-1.58s		1.59-2.06s		2.07-5.61s	
Recommended Starting Weight Range (lbs)	KE	KF	KE	KF	KE	KF	EE	EF	EE	EF	EE	EF
	19-30	10-15	18-24	9-14	9-20	4-9	4-5	8-9	4-5	6-8	2-5	4-7
4-week Training **Phase II**	0.80-0.94s		0.95-1.16s		1.17-1.99s		1.24-1.35s		1.36-1.73s		1.74-3.03s	
Recommended Starting Weight Range (lbs)	KE	KF	KE	KF	KE	KF	EE	EF	EE	EF	EE	EF
	20-33	14-19	21-28	10-15	12-24	10-14	5-7	10-11	3-6	7-10	3-5	6-9
4-week Training **Phase III**	0.78-0.93s		0.94-1.05s		1.06-1.75s		1.16-1.24s		1.25-1.69s		1.70-4.87s	
Recommended Starting Weight Range (lbs)	KE	KF	KE	KF	KE	KF	EE	EF	EE	EF	EE	EF
	21-37	13-20	19-35	11-17	17-29	11-16	6-8	11-13	3-7	9-12	4-6	8-11

Key: KE=knee extension, KF=knee flexion, EE=elbow extension, EF=elbow flexion

In view of these facts, moderate exercise for people with CMT would appear to have multiple advantages. But the correct method to achieve the greatest benefit from an exercise program is still not clear. People with CMT who have milder weakness appear to gain more from their exercise programs than those with more significant weakness. Strenuous training programs are more likely to cause mechanical or orthopedic injury and to produce a negative outcome. And the programs with the best results appear to be geared toward improving function, especially improving activities of daily living (Kilmer, 2002).

Prescribing an individualized exercise program for the CMT patient is

possible, based on assessments of performance of activities of daily living. A published report (Chetlin et al., 2004*b*) outlines a template for exercise that can be used by physiologists or physical therapists to design an appropriate exercise program for someone with CMT. Results are based on stopwatch-timed performances of a few simple functions of activities of daily living, including rising from a chair (sitting to standing) and rising from lying flat (supine) to sitting (Table 1). The goal is to then develop for each individual a program that will be safe, convenient, effective, inexpensive, and easy to design and implement (Table 2).

Many unanswered questions remain about the use of exercise by people with CMT. Most studies that have been done have looked solely at people with CMT Type 1A. No studies have looked at long-term (duration of one year or longer) exercise programs to determine whether consistent exercise continues to produce a positive effect. No studies have been published based on research from observing the effects of regular exercise and activities in children with CMT, although a small study is currently underway that is attempting to determine whether weakness can be delayed through a regular exercise program. Also, the possibility that CMT patients might be at higher risk for heart disease and diabetes needs to be explored further. Is there some component of CMT that might prevent or make it more difficult to reduce these disease risk factors? Or is it just decreased activity due to the weakness from the disease that places CMT patients at higher risk for heart disease and diabetes? Despite these unanswered questions, people with CMT should not be afraid to exercise in moderation, being careful to avoid orthopedic injuries, especially if they employ a personalized exercise program that addresses their specific muscle weakness pattern.

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CMT—The Family Disease:

Genetics Counseling and Related Issues

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Inherited conditions, by their very nature, affect not only those who are diagnosed, but their children, parents, siblings, and extended family as well. Having an inherited disease pass through the family often shapes the very identity of that family for many generations. Just as with any of life's challenging issues, families cope with having an inherited medical condition in a variety of ways, ranging from constructive and open to destructive and secretive. Some families with this diagnosis are able to communicate with one another about their condition and its challenges, and family members are able to make informed decisions about their futures. Other families may operate in secrecy as some members deny the existence of the problem or cannot understand why all family members do not cope in the same way.

The unique issues that arise in genetic disorders necessitate that the therapeutic approach to the patient with an inherited condition is often different from that applied to other patients. A detailed family history must be obtained, the risk to other relatives considered, and family planning options need to be discussed; the emotional issues that arise with familial diseases must be sensitively addressed. A careful evaluation of a patient with a potentially inherited disorder can be extremely time consuming for the busy primary care physician and the neurologist.

One way for physicians to deal with these issues is to extend the multidisciplinary approach to the care of those affected with inherited neuropathies so as to include counseling in genetics. For quite a long time, the need for a multidisciplinary approach to the care of patients with inherited neuropathies has been recognized. For example, the availability of physiatry, physical and occupational therapy, and pulmonary support have greatly contributed to patient care. Similarly, the involvement of a geneticist or genetic counselor can greatly enhance the ability of the physician to provide quality care to patients with inherited disease. Many primary care physicians and neurologists have not had the opportunity to work with genetic counselors and may not be familiar with the role that they play as part of a healthcare team.

What is the role of genetic counselors?

Genetic counselors are trained individuals who have a master's degree and a background in biology or the basic sciences. They are specifically trained in the care of patients and their families who have or are at risk for having a genetic disease. They typically work with other healthcare professionals, such as physicians, nurses, psychologists, and social workers. Genetic counselors help individuals deal with the complex issues that arise when the diagnosis of a genetic disease is made. Nondirective counseling is a basic tenet of genetic counseling, and those who work in this profession are dedicated to helping individuals make decisions about genetic testing, medical management, and family planning considerations that are in accordance with their lives and belief systems.

Counseling patients with inherited neuropathies also requires current knowledge of complex genetic issues, including the various types of inheritance patterns, questions of penetrance, anticipation, and

whether prenatal testing or preimplantation genetic diagnosis for various disorders is available.

An important component of the evaluation of the patient with a potential inherited neuropathy is the detailed family history, which is used to discover which other relatives may be at risk. Obtaining a detailed family history of at least three prior generations will often reveal symptoms in other family members that a patient may not have previously considered significant but which may be crucial for making a diagnosis. However, while a pattern of inheritance may emerge that can aid in making a diagnosis, the lack of evidence in a family history does not rule out a genetic condition. Often, it is necessary to obtain medical records on various family members to confirm a diagnosis, including more information about their prior tests in order to determine whether their condition is related to that of a specific patient. Obtaining these crucial medical records can be extremely time consuming, especially if the relatives are now deceased. Discussion of personal health issues within an extended family may be difficult, especially if communication within the family is otherwise strained. Patients must understand that it can be vital to share information about their condition with other family members.

Although many physicians are trained to give advice regarding prognosis and therapy, a nondirective counseling approach is necessary for handling many of the complex issues that arise when the diagnosis of an inherited condition is made. Patients with inherited conditions often seek further information about various decisions, including those regarding family planning. Prenatal testing, preimplantation genetic diagnosis, sperm and egg donation, adopting children, the decision to have children without any test results, and deciding not to have children at all are options that must be explored. Patients must be assisted in making the decisions that best fit with their beliefs, value systems, culture, and lifestyle without influence from any biases the clinician may hold. This approach can be difficult for the counselor, especially in the face of the inevitable

questions, such as, “What would you do?” Although it may be very easy and even tempting to answer this question with an opinion, it is important to keep in mind that that answer may not provide the best solution for that specific patient. Nondirective counseling is based on the belief that an individual is the only person who knows which decisions are best for her or him, and that individual has the right to make those decisions independently.

Genetic counseling services can be located by contacting the following:

- The National Society of Genetic Counselors at 312-321-6834 or at http://www.nsgc.org
- The public health department in your state- ask for genetic services
- A local medical center-- ask for genetic services

Basic genetics

Charcot-Marie-Tooth disease (CMT) occurs when there is a change, called a *mutation,* in the body’s blueprint that makes up the nerves. These blueprints, called *genes*, control not only the way a body is made, but also what it looks like and how it works. Most genes come in pairs. One gene of each pair comes from the mother’s egg and the other from the father’s sperm. In the one-hundred thousand gene pairs, sometimes one will be changed. Occasionally, a mutated gene will not cause problems. But, sometimes a gene with a mutation will cause some part of the body not to work correctly, and that person will develop a genetic condition, such as CMT. A gene mutation is usually inherited from one of the parents and may have been in the family for many generations. In some cases, the change in the gene occurs for the first time in the affected individual. This first-time change is called a *new mutation*. Although this new mutation was not inherited from the parents, he or she can pass this mutation to his or her children (Figure 1).

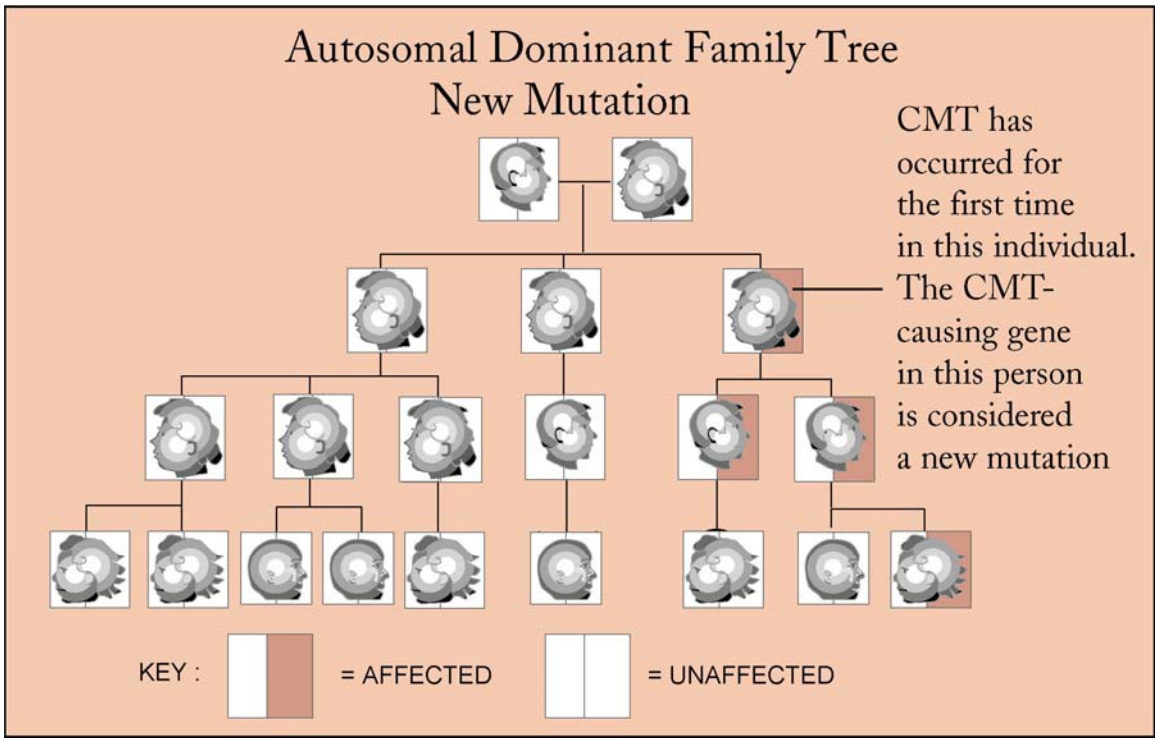


Figure 1. This family tree illustrates a new mutation. The children of this person all had a 50 percent chance of inheriting the CMT-causing gene and passing it on to their children. Members in the other branches of the family do not have an increased risk of developing CMT or passing it on to their children.

Genes are organized on *chromosomes* (Figure 2). Most individuals have 46 chromosomes in each cell in their bodies. The chromosomes come in 23 pairs, and the first 22 pairs are identical in males and in females. One member of each pair comes from the mother and the other from the father. The last pair is the sex chromosomes; females have two X chromosomes (Figure 2A), while males have one X and one Y chromosome (Figure 2B). Females receive an X chromosome from both their mother and father, while males receive an X chromosome from their mother and a Y chromosome from their father. *DNA* is the building block of the gene and is made up of four chemical bases represented by the letters C, T, G, and A.

The chromosome can be thought of as being constructed like a bookcase, and the genes are the many books located and organized

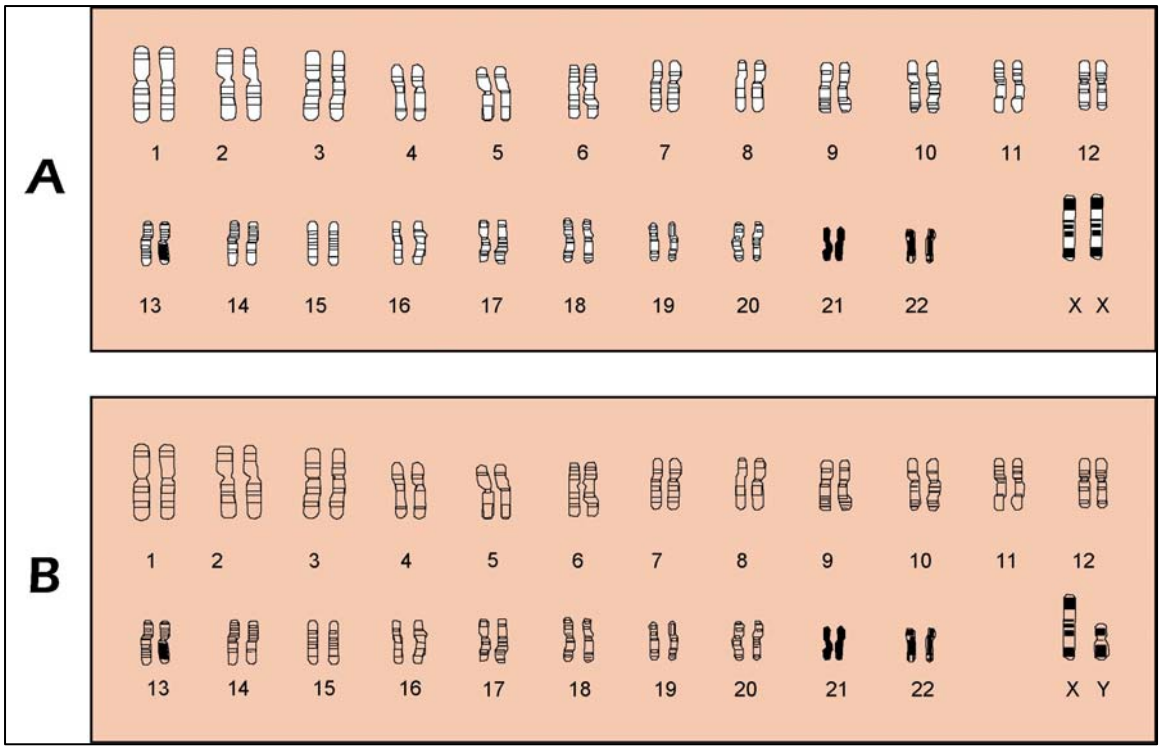


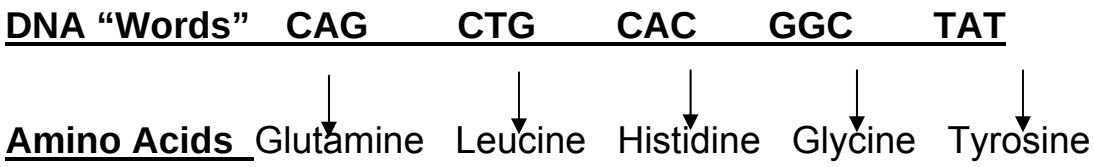
Figure 2. **A**) A set of 46 chromosomes from a female arranged in 23 pairs. The last pair, XX, determines gender. **B**) A set of 46 chromosomes from a male arranged in 23 pairs. The last pair, XY, determines gender.

on the bookcase. The DNA is like the letters of the alphabet which, when put together, give the book its meaning. However, if there is a typo in the book, or perhaps it has missing or extra pages, the meaning of the book's message might be changed. A mutation in the DNA of a gene is like a typo in a book.

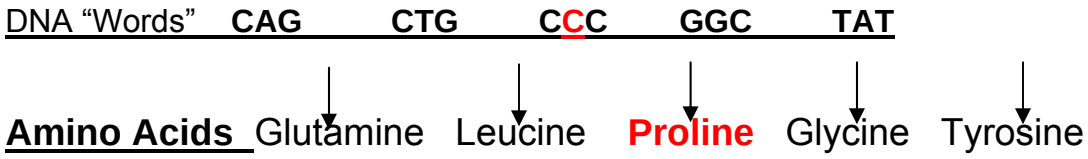
A mutation anywhere in the gene "book" can cause it to function in an improper manner. As it turns out, many different mutations within the same gene are usually found among different families, all of which cause the same genetic condition. This occurs in instances of CMT. However, the same mutation will always be found in individuals within the same family. Rare cases are reported of two different mutations (for two different types of CMT) in the same patient. Although these cases have been documented, they are not typical.

Different types of mutations can occur in the various types of CMT. A mutation that affects only a single base (one letter) is called a *point mutation.* Other types of mutations can include *insertions* (additions of the DNA alphabet into a gene), *deletions* (removal of part of a gene), and *duplications,* in which entire genes are present in one or more additional copies. The instructions contained in the DNA are needed for the body to make *proteins*. Proteins are the building blocks for various tissues, and there are more than eight proteins that are combined to make myelin in the peripheral nervous system.

A normal DNA sequence may look like the following:



When there is a point mutation, i.e., when one DNA letter is changed, it may cause an amino acid to be changed, as in the following example. This alters a protein and usually causes disease.



Inheritance patterns

Autosomal dominant

Most forms of CMT, including all of the CMT1 and CMT2 subtypes, are inherited in an *autosomal dominant* manner (Figure 3). Autosomal means the condition can equally affect males and females. In a dominant condition, a person needs to have a mutation in only one copy of the gene pair for the condition to be physically expressed. A parent who has an autosomal dominant gene has a 1 in 2, or 50 percent, chance of passing the gene on to her or his children, regardless of gender. The child who inherits the gene may

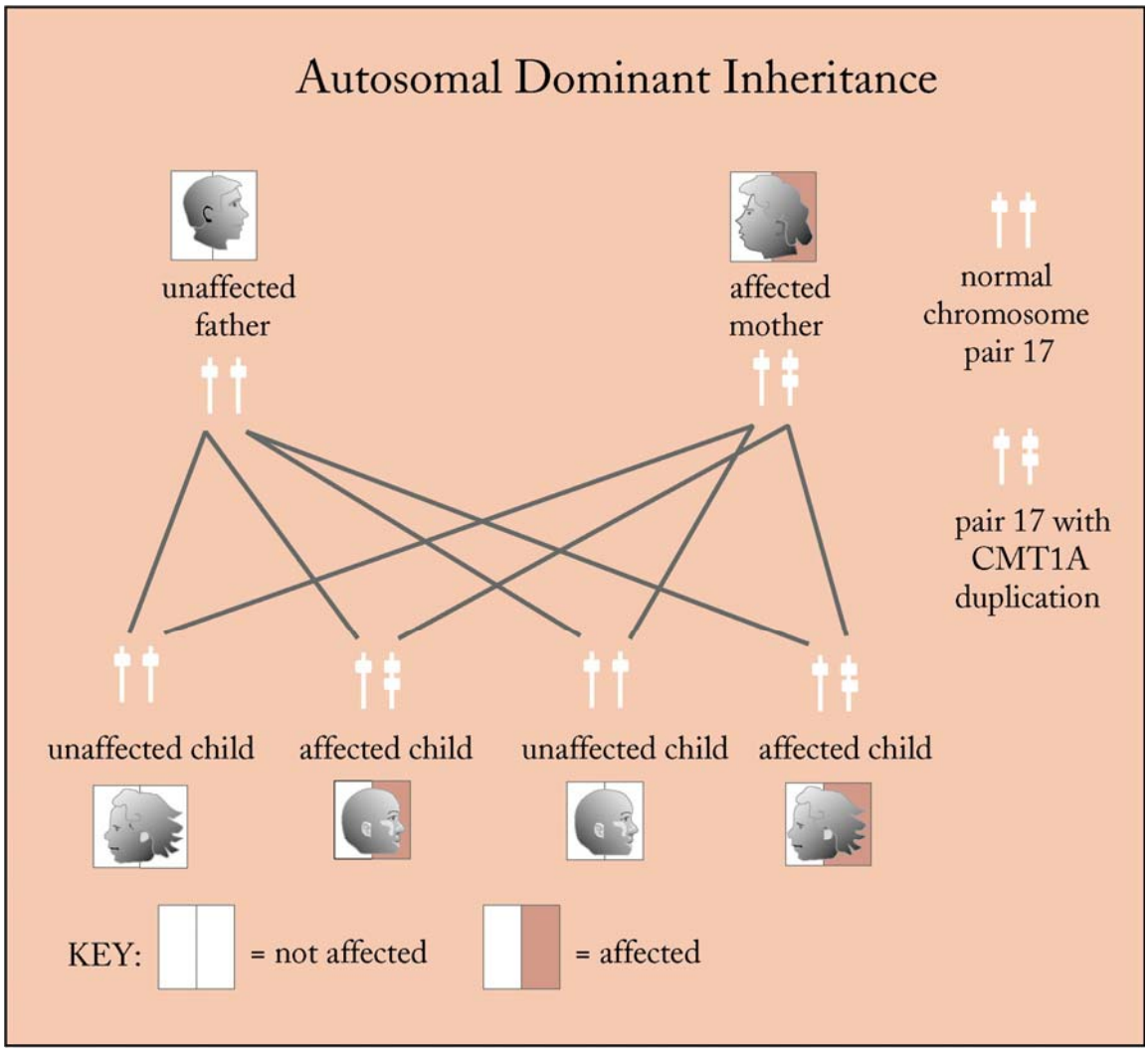


Figure 3. Autosomal dominant inheritance. Each child of an affected individual has a 50 percent chance of inheriting the CMT-causing gene. Unaffected people cannot pass CMT on to their children. Note that males and females have an equal chance of being affected with CMT.

have symptoms similar to or possibly more severe or less severe than those of the parent. This is called *variable expression* and is commonly observed in autosomal dominant conditions such as CMT. On the other hand, children who *do not* inherit the CMT gene will *not* develop CMT and cannot pass it to their children.

X-linked dominant

The gene that causes CMTX1 is called *GJβ1* and is located on the X chromosome. Therefore, CMTX1 is inherited in an *X-linked dominant* pattern (Figure 4). Because females have two X chromosomes, they

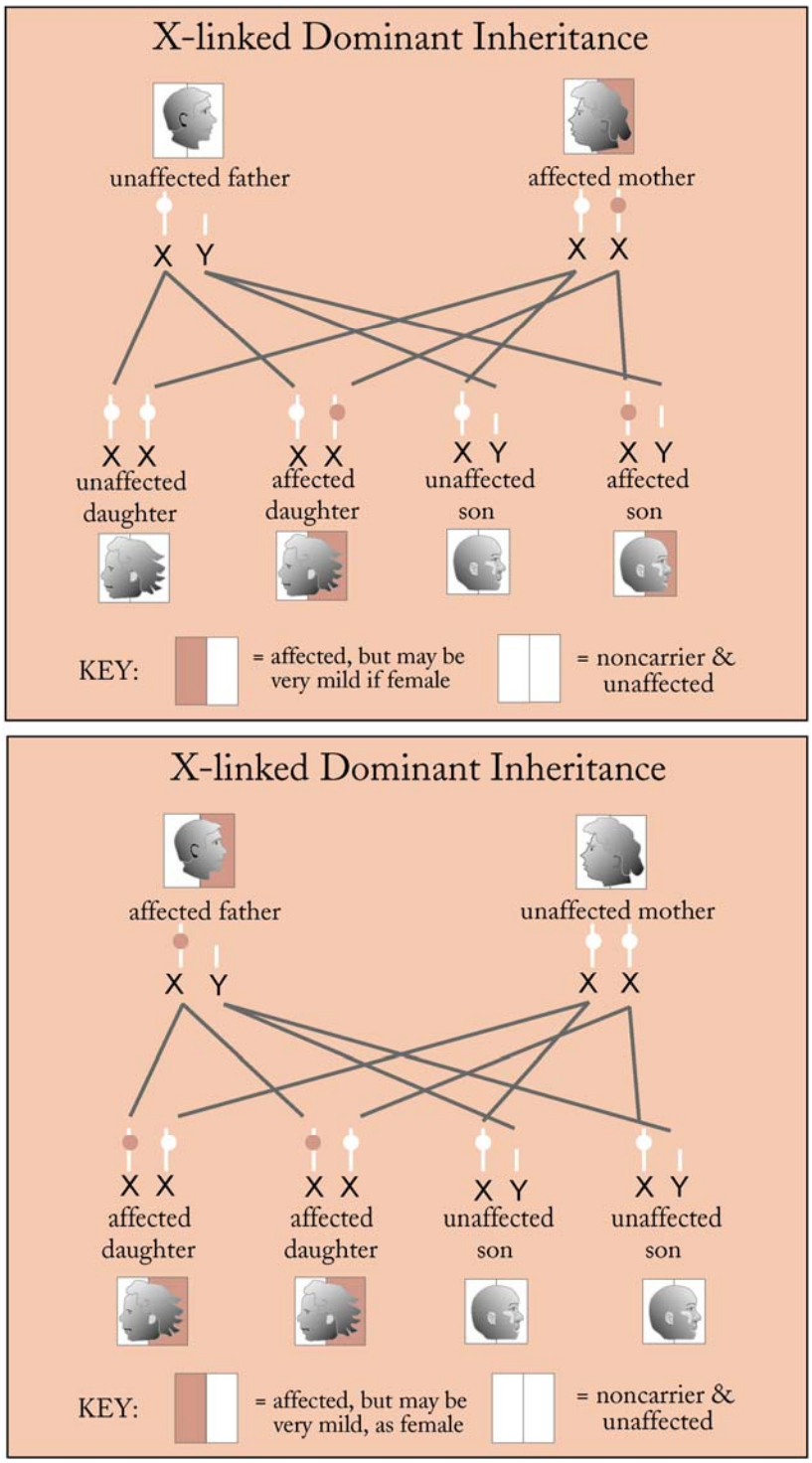


Figure 4. X-linked dominant inheritance. Although this type of inheritance is called dominant, affected females may have very mild symptoms that can go undetected. **A**) Affected females have a 50 percent chance of passing the CMT causing gene to all of their children. **B**) Affected males always pass the CMT causing gene to their daughters but never to their sons.

have two copies of the *GJβ1* gene. Males have one X and one Y chromosome and therefore they have only one copy of *GJβ1*. In families with CMTX, the affected males usually have more significant symptoms than affected females. In fact, females who have a mutation in one of their *GJβ1* genes may have very mild symptoms that can go unnoticed, although sometimes women can be just as affected as the men in their families. Some of this variability is likely due to the phenomenon of random X inactivation in females. This occurs early on in development when one member of each X chromosome pair is randomly "turned off." If the X chromosome containing the *GJβ1* mutation is more often inactivated in the cells that become the peripheral nervous system, then a female may be more mildly affected and conversely, if the X chromosome with the mutation is left "on" more often in cells that become the peripheral nerves, then a female may be more significantly affected. There are likely to be other factors involved in the extent to which a female experiences CMT symptoms, and there is no way to predict how significantly a specific female will be affected.

Females pass one or the other of their X chromosomes to their daughters and one or the other to their sons (Figure 4A). Women who have a mutation in one of their *GJβ1* genes therefore have a 1 in 2, or 50 percent, chance of passing it to either their sons or daughters. A son who inherits the mutation will eventually develop CMT, but a female who inherits the mutation may or may not develop significant symptoms.

Males pass their X chromosome *only* to their daughters and their Y chromosome *only* to their sons (Figure 4B). Therefore, in a family with CMTX, a father can never pass the condition to his sons, but will pass it to all of his daughters. The sons will not be affected and cannot pass CMTX1 to their children. The daughters may or may not have significant symptoms but could pass it to their children.

Autosomal recessive

The subtypes of CMT4 are inherited in an ***autosomal recessive*** manner (Figure 5). This means that two nonfunctioning copies of a gene are needed to cause the disorder; one gene mutation must come from *each* parent. A parent who has one normal gene and one gene with a mutation is called a *carrier.* Carriers usually have no symptoms or characteristics of CMT. Two carrier parents have a 1 in 4, or 25 percent, chance with each pregnancy to have a child affected with an autosomal recessive condition. Persons affected with the autosomal recessive form of CMT will pass one copy of this gene to each of their children. If that person's partner is not a carrier of CMT,

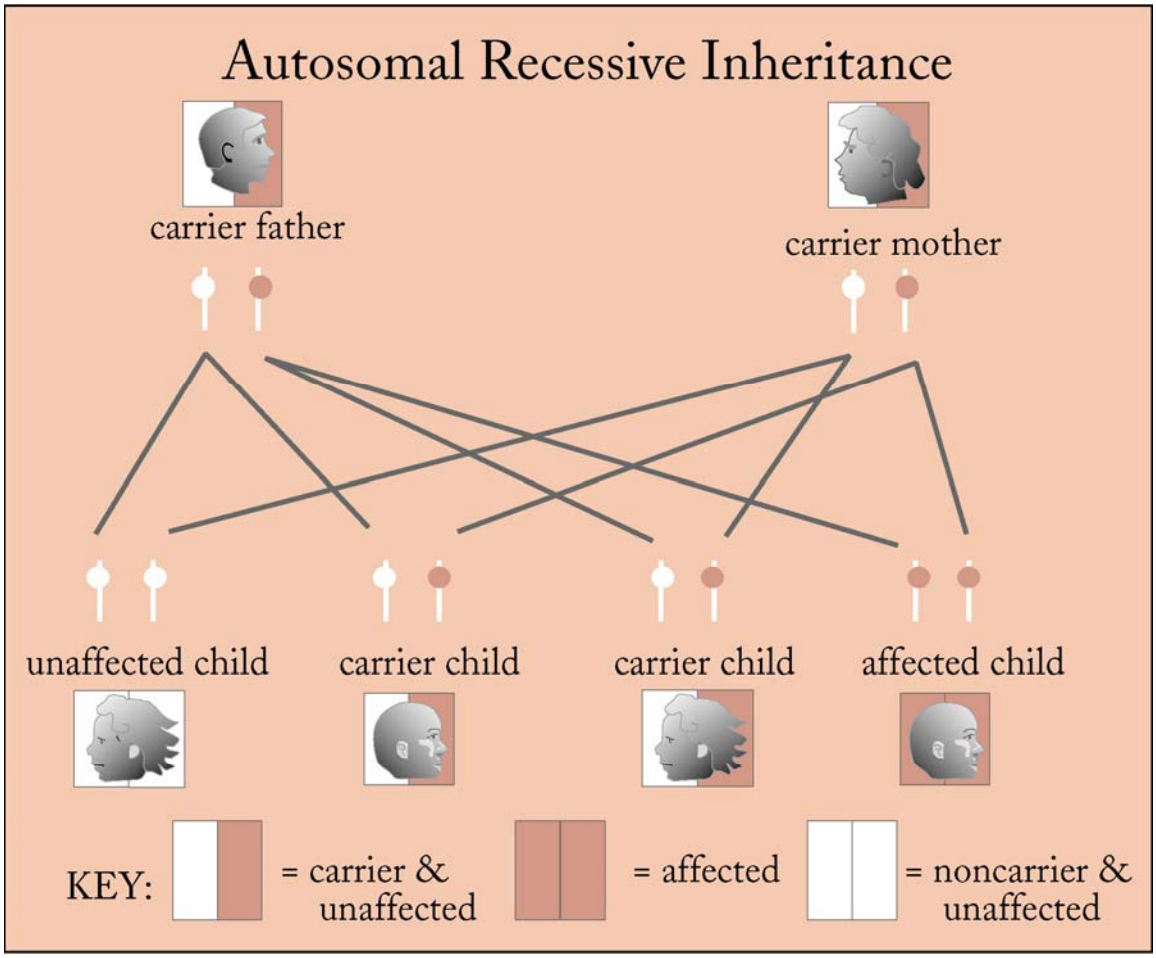


Figure 5. Autosomal recessive inheritance. Two carrier parents have a 25 percent chance of having a child with CMT. A person who is a carrier does not have CMT. Note that both males and females can be equally affected with CMT.

none of the children will be affected. All of them, however, would be carriers. If the partner is a carrier (probably very unlikely), then the couple would have a 1 in 2, or 50 percent, chance of having a child with CMT.

Genetic testing

After a gene and its associated mutations have been identified, researchers can develop genetic tests to offer to individuals who may be affected or at risk for CMT. Sometimes genetic testing helps to determine or confirm a specific diagnosis; at other times, it helps to answer questions for other family members. The process of obtaining genetic testing can be very complicated. Because various mutations in different genes can cause CMT among some families, it is important to determine which mutation is present within a specific family. Ideally, tests should be performed first on a family member who is clearly affected. If the mutation causing CMT is identified, the diagnosis is confirmed and other family members can be offered testing for that same mutation. If the mutation cannot be found, either the affected person does not have CMT, or they have it, but the mutation in that family cannot yet be identified. In this situation, other family members will not benefit from genetic testing. Since progress in genetic research is continuously developing, it is important to stay in contact with the CMTA or a genetics counselor in your geographic area for information on genetic tests for CMT.

There are many reasons for people to consider genetic testing. One important reason is to establish a diagnosis. Because the symptoms of CMT can be seen in other neurologic conditions, doctors sometimes cannot be completely certain of the diagnosis. Genetic tests, if the results are positive, establish a definitive diagnosis, which helps doctors to better answer patients' questions and provide appropriate treatment and management options. Unfortunately, there is no cure for CMT, and an awareness of the diagnosis will not change the course of the disease. However, clinical trials are

beginning for certain types of CMT, and in the future, various treatments might be available for specific types of CMT. In addition, a genetic diagnosis in one family member can provide answers to questions other family members may have. It may help to explain some of their medical symptoms or give them information about their own chances for developing CMT and the chances of passing it to their children. It also gives some family members the option of prenatal diagnosis in order to determine whether their developing baby will have CMT. Lastly, some people choose to have genetic testing in order to help doctors and scientists to better understand CMT. Further knowledge about the genetic causes of CMT will lead to greater insights into this condition, to better treatments, and ultimately to the hoped-for cure.

Although genetic testing can answer many questions, the results of the test also can raise new questions that impact other areas of a person's life. Questions arise about who will have access to genetic information and how it will be used. Some people have been denied health insurance, others have lost jobs, and some have been turned down for adoptions—all due to results of genetic tests. This is most disconcerting for people who find out they have the gene for a specific genetic condition but have not yet developed symptoms. Unlike other medical tests, the results of a genetic test may imply a serious diagnosis in other family members who may or may not want to be aware of their diagnosis. The decision to have genetic tests is a personal one that can only be made if one has a full understanding of the pros and cons. For this reason, genetic counseling fulfills an important role in the genetic testing process.

Commercial testing versus research testing

In the choice in favor of genetic testing for any given patient, testing for the most common types of CMT that fit with the person's history, examination, NCVs, and family history should be considered. However, if all potential types of CMT that are discernible by

commercial testing have been ruled out, testing may be considered for its research value.

New CMT-causing genes are usually identified in research laboratories, which are typically located at universities. When a research laboratory identifies a gene of interest, they usually seek out families who are potential candidates for having mutations within the gene. These laboratories can be selective about which families they agree to test or study. There is usually no fee for these tests, but there is no guarantee how long it will take for results, given that these laboratories often depend on outside funding and their interest and ability to pursue various projects may change over time.

After a test for a particular type of CMT has been developed in a research laboratory, commercial laboratories will often begin to offer the testing for a fee. When a test is done in a commercial laboratory, there is usually an established turnaround time for results. In the United States, commercial laboratories have to meet certain standards set by the Clinical Laboratory Improvement Amendments of 1988 (CLIA). This means that the laboratory had to pass certain standards to ensure the accuracy and reliability of its results. Since research laboratories do not have to meet the same standards as commercial laboratories, it is usually recommended that all results that come from a research laboratory should be confirmed eventually in a commercial laboratory after the testing becomes commercially available.

Reproductive options

If a CMT-causing mutation is identified in an individual or a family, a few reproductive options may become available. Because treatment or cure of an affected fetus is not yet possible, the current options involve selecting affected embryos or altering the course of a pregnancy based on the disease status of the fetus. The availability of these options for a condition such as CMT, which does not typically

affect lifespan or intelligence, can be controversial. However, patients should be aware of the options that are available to them, and they should be encouraged to make those decisions that are best for them and their families. Patients who are interested in any of the available procedures should be highly encouraged to seek genetic counseling prior to becoming pregnant because the availability of these options can change. A genetic counselor can discuss the details of the currently available options with the patient. Making arrangements for some tests can also take time, which, if a patient is already pregnant, can further complicate the process.

Prenatal testing

Prenatal testing is done during pregnancy to determine if a developing baby carries a specific condition, such as CMT. This test is generally only available to families for whom the specific type and/or mutation has been identified. If test results show that the developing baby is carrying the condition, the parents have the option to terminate the pregnancy.

Two choices are currently available for prenatal testing. The first is a procedure called *chorionic villus sampling* (CVS), which involves removing a very small piece of the placenta at 10 to 12 weeks into the pregnancy. The cells from the placenta are grown and analyzed for the presence or absence of the mutation. This procedure involves a low risk of miscarriage but should be performed by an experienced doctor. The other option is a procedure called *amniocentesis,* which involves removing a small amount of the amniotic fluid or water from the uterus surrounding the developing fetus. This test is typically performed between 15 and 18 weeks into the pregnancy. The cells in the amniotic fluid that have been shed from the skin of the developing baby are tested and analyzed for the mutation. This procedure involves a low risk of miscarriage and should be performed by an experienced doctor.

Preimplantation genetic diagnosis

Another procedure called *preimplantation diagnosis (PGD)* uses in vitro fertilization techniques to assess whether a baby will have CMT. The exact procedures vary somewhat depending on the laboratory where they are performed. However, it generally involves placing the woman on fertility drugs so that she will ovulate a number of eggs that will be removed and fertilized in the laboratory with the father's sperm. The number of eggs produced and retrieved and the number of embryos that form are dependent on several factors, including the age of the woman. When the embryos reach the 8- to 10-cell stage, one of the cells from each is removed and examined for the presence of the CMT-causing mutation. Only unaffected embryos are implanted into the woman, which virtually guarantees that the baby would be born free of CMT. Only a few centers in the United States perform PGD. While it may be advantageous for a patient to work solely with the center performing the PGD, it is often possible for patients to work with a local fertility clinic that can coordinate with the PGD center so that the patient does not need to travel. PGD typically costs many thousands of dollars and is not usually covered by insurance. Patients who are interested in PGD should be encouraged to contact various PGD centers for more information.

Other options

Many people with CMT would prefer not to pass the condition on to their children but would not consider terminating a pregnancy and would find the cost of PGD to be prohibitive. A few other options for family planning could be considered. If a man is affected, using sperm from a donor without CMT is a possibility. Although it would be more expensive than using donor sperm, a woman with CMT could choose to use a donor egg. Another choice is adoption. Because CMT does not generally interfere with a person's ability to be a parent, the condition is not an obstacle to adoption by most eligibility standards. Some people choose to have children without having tests, while others make the decision to remain childless.

These personal decisions are highly subjective, and patients need to carefully consider what will work best for their own lives.

Questions about CMT

If a family member of a person with CMT does not have symptoms, are they at risk to have a child with CMT?

Unfortunately, there is no a simple yes-or-no answer to this question. We must consider the following:

1. If the family member has been genetically tested and found *not* to have the gene mutation that is *known* to be causing CMT in the family, then the condition cannot be passed to their children. Remember if one does not inherit the CMT gene from a parent, he or she cannot pass it to a child.
2. Without the results of genetic testing, the answer is less clear. Although one may not show any signs of CMT, he or she might still have mild signs that are not obvious. That person should be examined by a neurologist familiar with CMT, who can determine whether he or she has mild signs.
3. The age of the person can also be relevant. Sometimes the symptoms of CMT do not begin until the adult years. Researchers have yet to determine the age at which symptoms can develop.

Why are some people in a specific family severely affected while others only have mild symptoms?

In families with CMT, every affected member of the family has the same genetic mutation. Therefore, it would seem logical that everyone would have the same symptoms. However, this is not what is observed with CMT and most other autosomal dominant disorders. Again, this is called variable expression. The reasons for differences among affected family members are unclear. The possibility also exists that environmental factors such as exercise and diet play a role. It is also possible that other genes have an influence on the severity of symptoms (although they do not directly cause CMT).

Although progress in the knowledge about the genetics of CMT is increasing, much more is still to be learned.

A patient appears to be the only person with CMT in the family; what is the explanation?

When only one person in the family is affected, there can be several explanations:

1. Possibly one of their parents is affected but has such mild signs that they have never been diagnosed. It is not uncommon for people with mild symptoms to be diagnosed only after someone in the family with more significant symptoms has been diagnosed. If the person's parents are living, it is possible for them to be checked by a neurologist familiar with CMT and perhaps to have genetic testing. If one of the parents has CMT, there are implications for other family members. Other children and the parent's brothers and sisters and their children could also have CMT. If both parents are deceased, it is very difficult to determine if either had the CMT gene mutation.
2. The patient has a "*new mutation*." This means that the mutation occurred for the first time in the patient, probably around the time of conception. The occurrence is random and is unlikely to have been caused by environmental factors such as smoking, medication, or exercise. It is difficult to estimate how often new mutations occur, but it is not uncommon in CMT type 1A. The patient's brothers and sisters are at low risk for developing CMT. Even if the patient's relatives do not have CMT, they can still pass CMT to their children.
3. The CMT could be inherited in an autosomal recessive pattern in this patient (see section on autosomal recessive inheritance). Remember that in instances of autosomal recessive inheritance, the condition is usually only seen in one group of brothers and sisters in a family. Someone who is affected with an autosomal recessive form of CMT probably has a very small chance of passing CMT on to his or her children.

Should children be tested for CMT?

The answer to this question is one that parents have to decide based on what they believe is best for their child. However, some factors should be considered. Parents may first choose to have the child examined by a doctor familiar with CMT to determine whether he or she is showing symptoms of the condition.

If a child is showing symptoms of CMT, it is reasonable to have testing performed. To know the cause of a child's physical problems is helpful for many reasons. Specifically, a definitive diagnosis will rule out other causes of symptoms.

If the child does not have symptoms, the tests will yield limited benefits in view of the fact that no treatment or cure for CMT is available. Restrictions may be unnecessarily placed upon a child's activities, thereby limiting her or his achievements. Also, children may be unfairly labeled by their "gene status" and difficulties could arise in the future around obtaining health and life insurance and employment. Although the results of genetic testing would determine the chances of passing CMT on to their children, it may be better to let a child make an independent decision at adulthood.

Resources in genetics

Research in genetics and genetic conditions is advancing rapidly, which poses a challenge to the clinician who must stay abreast of current information. Even textbooks can become obsolete shortly after they are published. Various online resources can aid in getting the most current, up-to-date information about neuromuscular conditions, clinical trials, and the availability of genetic tests. Many patients will be able to do significant research on potential or established diagnoses by using the Internet. The following websites may be useful to the clinician:

National Society of Genetic Counselors (NSGC) – http://www.nsgc.org This website for the professional organization for genetic counselors has contact information for genetic counselors in various disciplines throughout the United States. Information about genetic counseling is also available on this site.

GeneClinics – http://www.geneclinics.org This website offers detailed information about the availability of genetic testing, genetic conditions, and contact information for genetics services providers such as laboratories performing PGD. Only laboratories and clinics that choose to register are listed, but the listings are typically quite comprehensive. Thorough reviews on numerous genetic conditions written by experts in the field are also available and are regularly updated. The reviews are aimed toward medical professionals, but they are not overly technical. A glossary is included, along with explanations of various key words and concepts.

Online Mendelian Inheritance in Man (OMIM) – http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM Thousands of entries on genetic disorders and genes can be found on this website. The information listed here tends to be technical and contains summaries of significant findings in the published literature.

PubMed – http://www.ncbi.nlm.nih.gov/entrez/query.fcgi This website lists citations from biomedical literature.

National coalition for heath professional education in genetics – http://www.nchpeg.org This website provides information on genetics advances and genetics health information.

Genetic Alliance – http://www.geneticalliance.org The Genetic Alliance is an international coalition of millions of individuals with genetic conditions and more than 600 advocacy, research, and healthcare organizations that represent their interests. Their website

provides access to links for support groups for many genetic conditions and other genetics-related sites.

Inherited peripheral neuropathies mutation database – http://www.molgen.ua.ac.be/CMTMutations/default.cfm This database contains detailed information on all of the published papers on mutations that cause inherited peripheral neuropathies, including references.

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Medication-Induced Worsening of Neuropathy in Charcot-Marie-Tooth Disease

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Although medication-induced neuropathy accounts for only an estimated 2 percent of peripheral neuropathy cases, it is an important cause of potentially reversible neuropathy. Simply stopping the agent is the intervention in most instances, although incomplete or delayed recovery can occur when nerve injury is more severe. This area of study is continually changing—new medications that were not initially known to cause neuropathy continue to be approved, and their association with toxic neuropathy are found only later—after they have been in widespread use. For example leflunomide was approved in 1998 as a novel treatment for rheumatoid arthritis. Peripheral neuropathy was not identified in studies prior to its release, but a review six years later uncovered 80 cases of probable leflunomide-induced neuropathy. A considerable number of agents are suspected of causing peripheral neuropathy. Some have been definitively proven and many have, at best, a tenuous or doubtful link based on outcomes among a very small number of patients. Especially difficult to prove are causes that develop slowly with extended drug use.

Existing peripheral neuropathy is a generally accepted risk factor for susceptibility to neurotoxic agents, including Charcot-Marie-Tooth disease (CMT), but the association has not been rigorously studied. Other genetic traits are known to affect peripheral nerve vulnerability to toxins. More pertinent to clinical neurology, however, is whether certain medications are unduly hazardous to patients with hereditary neuropathies, especially CMT), which is a common disorder that affects approximately 150,000 Americans. Should CMT patients avoid certain medications, even if clearly indicated, because of concerns of neurotoxicity? Also unclear is whether CMT subtypes have different sensitivity to certain medications—concerns for CMT1A may not apply to less common subtypes. The Charcot-Marie-Tooth Association (CMTA) has long maintained a list of potentially hazardous medications for patients with CMT and treating physicians to consult. This list is extensively accessed and potentially could deter the use of a preferred medication for an unrelated condition because of inordinate perceived risk. The list includes 25 medications and vitamins. It is published in the CMTA's newsletter, *The CMTA Report*, and appears on its website (http://www.charcot-marie-tooth.org/med_alert.php). This website was accessed 2,012 times during a one-month study period, supporting the fact that it serves a wide audience.

In order to assess current direct knowledge of CMT patient experience with medications, two approaches were used—an extensive literature search and an examination of medication effects recorded in the CMT North American (CMTNA) database.

Medical literature

An extensive search of the medical literature identified exposures of patients to medications that are potentially neurotoxic. Despite the generally accepted concept of medication-induced worsening of CMT, only 26 reports were identified. Twenty-two of the reports addressed one agent that is well known to worsen CMT—vincristine.

The additional reports included two on nucleoside analogs used to treat HIV infection and two on other chemotherapy drugs, including cisplatin, carboplatin, and taxoids.

Vincristine, a widely used vinca alkaloid, is a first-line chemotherapeutic agent for several cancer types. The drug is the only one with multiple credible examples of inordinate toxicity in CMT patients, which can be severe and sudden, in some instances after one treatment. The link was first obvserved by Weiden and Wright in 1972 and by a few others in the mid-to-late 1980s. However, it was not until Graf and colleagues reported three cases in 1996 that the issue gained widespread attention. The 22 reports reviewed describe 30 affected patients.

For most patients in the general population, a minimum total dose of 5 mg to 8 mg is the described threshold for inducing sensory neuropathy; motor involvement usually results from higher dosages. In CMT patients, acute worsening or initiation of weakness, sometimes severe general weakness, occurred in 18 of the 30 reviewed by Graf after only 2 mg to 4 mg or the equivalent pediatric dose (1.5 mg/m^2/dose). Nearly all reports describe eventual improvement, but often not to original levels. Most cases had previously unsuspected and undiagnosed CMT (26 of 30). However, 10 of these cases had, in retrospect, clinical signs prior to treatment with vincristine (high arches, known as pes cavus, or foot muscle atrophy) or they were in a family in which a close relative had known CMT. Almost all patients had clinically compatible or genetically confirmed CMT1A (PMP-22 duplication); several reports were made during the years before genetic testing became available. One revealed the hereditary neuropathy with liability to pressure palsies (HNPP) PMP-22 deletion. One patient with a probable axonal form of CMT (type 2) developed moderately severe primarily sensory neuropathy following vincristine treatment but reportedly tolerated extended administration and recovered quickly.

Five reports were found that discuss exposures to other agents. A 23-year-old man with X-linked CMT developed mild neuropathy after treatment with cisplatin and adriamycin that was thought to be no different than if he did not have CMT. A 60-year-old woman with longstanding CMT and ovarian cancer developed worsened neuropathy after multiple doses of paclitaxel and carboplatin. After changing to docetaxel and carboplatin, she was able to complete her full therapy without additional neuropathy progression. The remaining reports address HIV medications in CMT and HNPP patients. Despite the long list of many other known or suspected medications linked to neuropathy, no other reports could be found.

CMT North American Database

The CMTNA database, initiated at Wayne State University and currently housed in the department of medical and molecular genetics at Indiana University, is a computerized registry tool derived from a highly detailed, nine-page questionnaire. Responses are from CMT patients and from treating physicians in neuromuscular clinics in the United States and Canada. This instrument offers abundant clinical information, including exposures to medications.

Analysis of database information stripped of patient identity data provided 996 drug entries on 209 persons from 190 families. Nineteen medications were identified by our criteria among the patients that indicated a perceived clinical worsening associated with a medication. The majority of reported adverse exposures occurred within one month. Medications with multiple exposures and more than one claim of symptomatic neuropathy worsening included metronidazole (Flagyl) (3 of 13 exposures), nitrous oxide (3 of 6 exposures), statins (2 of 20 exposures), nitrofurantoin (2 of 11 exposures), phenytoin (2 of 11 exposures), and sertraline (5 of 21 exposures); others (isoniazid, penicillin–high IV doses) had one or two adverse reports. Some had other complicating causes of neuropathy, including diabetes (nitrofurantoin) and inactive hepatitis-

C (metronidazole). Entries were also made for 150 exposures to anesthesia; 12 (8 percent) reported some degree of worsening but with insufficient details to study the connection further in specific individuals.

Genetic information was available for 22 persons in the study group, but no discernible disparity of one CMT subtype to one agent was noted; however, overall numbers are small.

Discussion

Should CMT patients avoid certain medications due to concern about neurotoxicity? Vincristine appears to be in a separate high-risk category for patients with demyelinating forms of CMT, including CMT1A, and, in all probability, HNPP. The possibility of acute worsening after a single dose makes even cautious administration problematic. Strong recommendations have been made that CMT patients should not receive vincristine; moreover, genetic testing for mildly symptomatic or asymptomatic patients at risk for the condition or patients with a compatible family history should be strongly considered prior to initiating treatment. The United States Food and Drug Administration has a standing, specific warning that vincristine injection is contraindicated in patients with the demyelinating form of CMT. Despite these warnings, cases of vincristine administration to patients with CMT1A continue to occur; most cases are discovered by reevaluation after perceived excessive toxicity or by a characteristic demyelinating neuropathy pattern revealed by subsequent testing. Why this inordinate toxicity occurs with this one gene defect and not others is unknown but worthy of further investigation. Inordinate vincristine effects on other forms of CMT are less clear but should be closely watched if no alternative drug is available.

Extremely limited data is available on other chemotherapeutic drugs, including adriamycin, cisplatin, carboplatin, docetaxel, and paclitaxel.

This limited experience seems inadequate as a basis for considering the drugs to be either safe or inordinately risky for appropriate use in patients with CMT. Of the agents discussed, taxoids are most prone to affect motor function, which is especially important in CMT; cisplatin, carboplatin, and oxaliplatin preferentially affect sensation.

Data from the CMTNA database should be interpreted with caution, but the data is of interest in identifying which medications are prescribed or not prescribed for CMT patients. Alternative antibiotics are available for most indications for these drugs, but not all. Metronidazole is the agent of choice in some instances, but it should be used with caution and for limited duration. Nitrofurantoin, used in some instances of urinary tract infection, is probably used best only if no adequate alternative is available to patients with CMT. Nitrous oxide inactivates vitamin B_{12} and can cause spinal cord and nerve injury (myeloneuropathy) in patients with borderline vitamin B_{12} levels or patients who chronically abuse the agent. The unexpectedly high percentage of cases listed in the database suggests that some patients with CMT experience worsening after nitrous oxide anesthesia. Verification of normal cobalamin levels, or ideally methylmalonate levels, should be considered in CMT patients planning to receive nitrous oxide anesthesia. Phenytoin (Dilantin) has been long associated with peripheral neuropathy, more prominently in earlier eras when considerably higher doses were used. The database listing suggests that the drug should be used with caution in CMT patients or used as one of several alternative agents for seizure control; however, patients who are well controlled on phenytoin should be considered individually. Two patients reported worsening following statin use. This issue is complicated by the more common condition of cholesterol lowering agent myopathy, alongside the controversial issue of statin-induced neuropathy. The benefits of these agents are well documented; however, use in CMT patients should be monitored both for onset of induced myopathy, which will cause additional weakness, and the probably uncommon

neuropathy. Historical descriptions, however, involve predominantly sensory function, and the link with neuropathy and statins remains controversial. Anecdotal but unpublished communications have noted an increase in symptoms with certain serotonin reuptake inhibitors (SSRIs), most commonly sertraline. The unexpected number of five entries in this series supports this association, although additional detail is needed to establish a stronger association. At present, no substantive literature in the general population is known that associates SSRI agents with peripheral neuropathy, but alternative SSRI agents are abundant. This association needs further study to determine whether it represents symptomatic worsening (pain) or a more objective neuropathy exacerbation.

Numerous other agents associated with neuropathy had no reports in this series. This suggests that either insufficient instances are documented or that the risk is minimally different from that in non-CMT patients. The data on anesthesia in general is problematic to interpret. Whether the effects listed as worsening are because of a true neuropathy exacerbation or because nonspecific effects of postoperative illness or reduced activity is not revealed by the available data.

Considerable disparity exists between the perceived risk of certain medications and the number of reports in the literature, other than for vincristine. There are several possible explanations, including the following: 1) the high-risk drugs are avoided in CMT patients unless the diagnosis is unknown; 2) examples of toxicity occur but are unreported; 3) most drug effects are uncommon and affect only a small percentage of CMT patients or affect nerve functions minimally affected by CMT; 4) worsening of neuropathy is an inherent process in CMT, and drug-induced worsening may be overlooked by both patients and clinicians; or 5) a combination of various possibilities. A number of drugs associated with neuropathy are listed in the

Table 1. Proposed list of medications of concern to patients with CMT

Definite High Risk (including asymptomatic CMT)

Vinca alkaloids (vincristine)

Moderate to Significant Risk

Amiodarone
Bortezomib (Velcade)
Cisplatin, Carboplatin, Oxaliplatin
Colchicine (extended use)
Dapsone
Didanosine (ddI)
Dichloroacetate
Disulfiram
Gold salts
Leflunomide
Linezolid (extended use)
Metronidazole/Misonidazole (extended use)
Nitrofurantoin
Nitrous oxide (inhalation abuse or Vitamin B12 deficiency)
Perhexiline*
Pyridoxine (high dose)
Stavudine (d4T)
Suramin
Tacrolimus (FK506, ProGraf)
Taxoids (paclitaxel, docetaxel)
Thalidomide
Zalcitabine

Uncertain or Minor Risk

Fluorouracil-5
Adriamycin
Almitrine*
Chloroquine
Cytarabine (high dose)
Cyclosporine A
Ethambutol
Etoposide (VP-16)
Gemcitabine

Uncertain or Minor Risk, cont.

Griseofulvin
Hexamethylmelamine
Hydralazine
Ifosfamide
Infliximab
Isoniazid (+ B_6)
lansoprazole
Mefloquine
Omeprazole
Penicillamine
Penicillin (high IV doses)
Phenytoin (Dilantin)
Podophyllin resin
Sertraline (Zoloft)
Statins
Tumor necrosis factor-α (infliximab, Remicade)
Zimeldine*
Interferon alfa

Negligible or Doubtful Risk

Allopurinol
Amitriptyline
Chloramphenicol
Chlorprothixene
Cimetidine
Clioquinil
Clofibrate
Enalapril
Fluoroquinolones
Gabapentin
Gluthethimide
Lithium
Phenelzine
Propafenone
Sulfonamides
Sulfasalazine

**Not available in the United States*

database records, but many are not; some were possibly avoided deliberately. Despite the continued uncertainty for most agents even after this review, drugs strongly associated with toxic peripheral neuropathy should be used with caution in CMT patients. In place of a single list, a collection of agents segregated into probable relative risk to CMT patients should be more clinically useful. Based on the information gathered in this study, combined with consultation of the general toxic neuropathy literature and methods used to determine the strength of association of toxic neuropathy in the general population, a revised and updated list is proposed (Table 1). Although this list is based on the best available information, determinations remain subjective to a degree; some may disagree with the category placement of some agents. As with any treatment, the relative risk of neuropathy exacerbation must be weighed against expected treatment benefits and available equivalent, alternative treatments.

Despite the limitations of this review and analysis, this study is likely the first comprehensive look at medication-induced exacerbation of neuropathy in CMT disease. Further research is needed to determine accurate relative risks for specific agents, if possible. A prospective study with direct objective evidence of neuropathy exacerbation is ideal, but that would be problematic to achieve. However, clinicians caring for CMT patients should consider current and potential medications for possible neurotoxicity and probable drug-induced exacerbations of documented neuropathy.

Summary and recommendations

Clearly, vincristine treatment is an unacceptable risk to patients with known or possible CMT1A and most likely HNPP. Prior to its use, a directed family history and screening for overt clinical signs of CMT is prudent; genetic testing may be indicated in suspected cases. Use of other agents in the significant risk category and use of vincristine in other CMT subtypes should be considered with caution; however,

this recommendation is based on very limited direct evidence in patients with CMT. Agents most commonly identified in the CMTNA database include nitrous oxide, metronidazole, nitrofurantoin, phenytoin, and, surprisingly, sertraline. The probable lesser risk of agents in lower- ranked categories should also be weighed when prescribing these drugs for patients with CMT. Increased awareness may lead to more frequent reporting of well-documented cases of agent-specific worsening for treatments other than vincristine, which may lead to further improved recommendations of risk with other agents.

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Resources for CMT Patients and Family Members

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Many people diagnosed with CMT feel as though they are all alone in dealing with their disorder. That should not be the case. There are several direct service providers who can help in providing proper medical care. There is a diagnostic DNA testing service available for CMT. There is information provided by non-profit organizations, such as the CMTA, and there are forums and chat rooms where even the most isolated person can connect with someone else who has CMT.

In this chapter, we will provide patients and family members with the information necessary to connect with the people and organizations who can help.

Direct Patient Care

In the direct patient care category, there are two well-known charitable organizations.

Shriners Hospitals for Children

The first is Shriners Hospitals for Children. Any child may be eligible for care at Shriners Hospitals if the child is under the age of 18 and there is a reasonable possibility the child's condition can be helped. There is never a charge to the patient or the parents for any medical care or services. For more information about Shriners Hospitals, visit www.shrinershq.org/Hospitals/_Hospitals_for_Children/. Application forms for admission to the orthopaedic hospitals can be downloaded

in Adobe format or obtained by calling the toll-free referral line at 1-800-237-5055. (In Canada, call 1-800-361-7256.) The hospitals offer a full spectrum of orthopedic care, including bracing, therapy and corrective surgery.

Shriners Hospitals (orthopedic) locations:

- Boston, MA
- Chicago, IL
- Erie, PA
- Greenville, SC
- Honolulu, HI
- Houston, TX
- Lexington, KY
- Los Angeles, CA
- Mexico City, Mexico
- Minneapolis, MN
- Montreal, QC, Canada
- Philadelphia, PA
- Portland, OR
- Sacramento, CA
- St. Louis, MO
- Salt Lake City, UT
- Shreveport, LA
- Spokane, WA
- Springfield, MA
- Tampa, FL

Shriners International Headquarters is in Tampa, Florida, and can be reached by phoning 1-813-281-0300.

The Muscular Dystrophy Association

The second voluntary health agency serving CMT patients of all ages is the Muscular Dystrophy Association. The MDA operates approximately 200 hospital-affiliated clinics across the country. In MDA clinics, a person receives diagnostic and follow-up care from specialists in neuromuscular diseases and can receive assistance with the purchase and repair of wheelchairs and leg braces, invitations to summer camps for youngsters and participation in support groups.

The only requirement for receiving an evaluation at an MDA clinic is the written recommendation of a physician who has determined the

person may have one of the neuromuscular diseases covered by the MDA's medical services program. (CMT is one such disease.)

MDA pays for only those services authorized in its program that are not covered by private or public insurance plans. Their payments are made directly to the institution in which the MDA clinic is located or to authorized vendors. No services or durable medical equipment may be ordered directly by the patient or their family if they wish the MDA to pay for the item or service.

In addition to the preliminary diagnostic process, the MDA clinics provide invaluable management care. They schedule annual follow-up visits and may prescribe physical therapy, occupational therapy or respiratory therapy (one consultation annually to evaluate the need and to instruct the patient or family in continuing therapy), social services to help patients find additional resources for payment of medical services, cooperation with the person's personal physician in the form of summary reports, genetic counseling, support groups and flu inoculations.

In those cases where family or community resources are not available, the MDA assists in arranging transportation to appointments at the nearest MDA clinic. For complete information about the services of the MDA, go to their home page at www.mda.org or call 1-800-344-4863.

CMT Clinics

Two other providers of direct patient care are the clinics at Wayne State University, Detroit, MI, and The John P. Murtha Neuroscience and Pain Institute in Johnstown, PA.

The clinic at Wayne State was founded in 1977 and has seen patients from the US and 12 other countries since its inception. In addition to providing clinical care, they also use the information

gleaned from patient evaluations to add to their clinical research studies on the natural history and progression of CMT and related conditions.

Initially a patient meets with a genetic counselor to talk about the study and the specific testing that will be done. Genetic issues related to CMT and options for genetic testing will be discussed. Tests that are done include sensory testing, strength testing, nerve conduction velocity testing, and hand function testing. A neurologist will evaluate each patient by reviewing their medical history and doing a neurological exam. A physiatrist will address possible rehabilitative needs such as bracing or physical and occupational therapy.

To make an appointment or to ask specific questions about the clinic, call 1-313-577-1689.

The Charcot-Marie-Tooth program at the John P. Murtha Neuroscience and Pain Institute was begun in August of 2003. The CMT specialists there take a team approach to CMT diagnosis. At the first visit, they take a medical history and a family history. Diagnostic tests such as neurological and physical exams, nerve conduction studies, electromyography and genetic testing may be done. One of the offerings of the clinic is a six-week program called “Healthy Living with a Chronic Condition.”

The staff at the Johnstown clinic work to blend traditional medical practices with proven complementary therapies as a means of improving the physical and emotional well-being of people with CMT.

A patient can refer him/herself or be referred by a doctor. For more information, call 1-877-576-5700.

Genetic Testing and Counseling

Genetic diagnosis of CMT is important when families are considering inheritance probabilities for future children and when the more traditional measurements, such as nerve conduction velocities and electromyeograms are inconclusive. Comprehensive genetic diagnostic testing is available from one commercial company: Athena Diagnostics, in Worcester, MA. Information about the testing procedure and the possible costs can be obtained by calling customer service at 1-800-393-4493, or by visiting www.athenadiagnostics.com. The tests must be ordered by a physician, but information can be gathered by patients before making any decisions regarding the tests. Currently, Athena offers tests for 1A, 1B, 1C, 1D (ERG 2), 1E, 1F, 1X, 2A, 2E, 2I, 2J, 2K, 4A, 4E, 4F, HNPP, CHN and DSN; however, the list is always growing.

In addition to the genetic testing, Athena also offers genetic counseling and test interpretation to physicians so that they can better serve their patients once the test information has been received.

Independent genetic counselors may also be located though the National Society of Genetic Counselors. Visit www.nsgc.org or call 312-321-6834.

Social Security Disability (SSD and SSI)

As patients age and the progression of CMT interferes more and more with their work, they often consider applying for social security disability. There are a lot of myths and misinformation about disability benefits from Social Security and the application process. This is generally undeserved because, while the Social Security Administration (SSA) is an extremely large bureaucracy, the application process is generally straightforward and usually customer friendly.

[This section, which explains the application process and provides helpful tips, was written by Jacques Chambers, who is an independent benefits counselor. He spent twenty-five years in the health insurance industry and the last ten years assisting people with their public and private benefits.]

First there are two primary programs for persons with disabilities, Social Security Disability Insurance (SSDI) and Supplemental Security Income (SSI), the former for workers and their dependents who have paid into the Social Security system through F.I.C.A. payroll taxes, the latter a program based on need. The process of applying for them is very similar.

There is a belief that it is very difficult to get disability benefits from Social Security. I've even heard it said "Social Security always turns you down the first time." Neither is true. It would seem to be born out by the fact that almost 2/3 of all applicants are turned down initially. However, this is not so much because the process is so difficult as it is that most people apply without any preparation or understanding of the process. Knowledge of the process and knowing how to track your claim through the process can make it easier and increase your chances of approval.

What does "disabled" mean? First, you need to know what standard Social Security uses to determine if someone is disabled enough to qualify for benefits. Whether it's SSDI or SSI, they define disability as*: "the inability to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment(s) which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months."*

The key to all that legal definition is *"the inability to engage in any substantial gainful activity…."* This means that Social Security is looking at functional problems. Lab numbers, names of diseases,

diagnoses are only used to support the fact that you are unable to work in any substantial manner. There must be physical or mental symptoms that prevent working and will last for at least one year.

For people dealing with CMT and other neurological disorders, SSA looks for a condition, either static or progressive, that produces any type of neurological impairment. This can include weakness, spasticity, uncoordination, ataxia, tremor, athetosis, or sensory loss. However, according to their regulations, "Documentation of motor dysfunction must include neurologic findings and description of type of neurologic abnormality." They want to know what the symptoms are and what causes them.

Social Security defines *Motor Dysfunction* as:

"Persistent disorganization or deficit of motor function for age involving two extremities, which (despite prescribed therapy) interferes with age-appropriate major daily activities and results in disruption of:

- Fine and gross movements, or
- Gait or station.

Note that they are not looking for any particular diagnosis. Being diagnosed with Charcot-Marie-Tooth without disabling symptoms will not generate an approval. They are looking for actual motor function problems that interfere with major daily activities. They need to see evidence of actual symptoms that prevent someone from functioning. For a child, that is activities that are age appropriate; for an adult, that usually means ability work perform substantial work, i.e. full-time work.

That doesn't mean that you have to be so disabled you can't do anything including selling pencils on a street corner. Generally, they look to see if you are able to do work that would be suitable for you based on your age, experience, training, and education.

Medical Records. Because they need to see evidence of functional problems, it is important that your medical records be detailed and complete. Social Security looks to your medical records as the primary source of that evidence. Therefore, it is important that, before you even start the application process, you sit down with your medical records and look them over carefully. How detailed and complete are they? Are there statements and comments about your condition that support an inability to work? Did the doctor report your statements about problems and list all the symptoms you reported? With doctors being pushed to see more and more patients, sometimes records aren't as complete as they should be to support a disability claim. If a symptom or functional problem is not reported in the record, then it's going to be difficult to get them to accept it as evidence of disability.

If your records are not complete in listing your symptoms, ask your doctor to write an extensive explanation of your condition, itemizing his observations plus what you have reported to him that wasn't included in your record.

Symptom Diary. Although it may be too late for the initial application, start a symptom diary immediately. This is simply a journal in which you write down all the symptoms that you have experienced each day. In addition to stating the symptom, describe the severity, list what its impact was on you and your activities. For example: *"So tired after trip to doctor, I had to nap for three hours." "I started to clean bathroom but was too tired to continue after cleaning the tub."*

Find a Friendly Office. Social Security offices develop their own personalities. Some are more difficult to deal with than others. This is a good time to put your grapevine to work for you. Talk to others from your support group or your doctor's office or others who have gone through the procedure. You can apply for Social Security Disability at any of their field or branch offices. When you call the national number to make the appointment (800-772-1213) you can

request which office you want the appointment made with. If you can find an office that has a reputation of being easier to deal with, go there. It really will improve your chances for approval.

Go to the Appointment Prepared. When you make your appointment to apply for Social Security, you will be given the option of applying by phone after they send you some forms to complete or of going into the office and applying in person. I recommend going into the office for two reasons. The Claim Representative is asked in their paperwork their impression of you and your functional abilities so if you have trouble walking or thinking clearly, the representative will observe and report it. Second, you are asked to provide original documents, such as your birth certificate. If you deliver it in person, they can see the original, photocopy it, and return it to you immediately so you don't risk losing valuable documents in the mail.

Take all the documents you are instructed to take. Normally this will include:

- Proof of birth. If you were born in this country they want to see an original or a certified copy of your birth certificate. (If you don't have one, go to the appointment; they will help you obtain one.)
- Military discharge papers, if any.
- Social Security card, or at least your Social Security number.
- Proof of residency, if you are a non-citizen.
- If you're applying for SSI, take bank records, housing documents, deeds, leases, etc. and other financial documents showing your assets and income.

There are other documents you can take which, although not required, will help speed up the process:

- Your Medical Records. Although they can get them from your doctors, it will speed up the process if you obtain copies of all your records and take them with you to the appointment.

- Your symptom diary if you've been keeping one.
- A letter from your doctor detailing your condition and presenting his or her observations about your ability to function at a job.
- Third party testimony. These are letters from people you live or work with that detail their observations of you and what they have seen as your ability to function deteriorated. Anecdotes about problems they have observed can be very helpful. A statement from a coworker or supervisor about increasing difficulties in performing your job can be especially persuasive.

The Consultative Exam. Occasionally an applicant will receive a letter announcing they have an appointment with a physician for a consultative exam. If you receive one, immediately call your Claim Representative—the name and number will be on the letter—and ask that your own doctor perform the exam instead. Consultative exams are notoriously brief and superficial and rarely provide support for a claim. Social Security's own regulations give preference to the attending physician's information so ask for a supervisor if you have trouble getting them to agree to using your own physician.

Spend Time Completing the Forms. When you first apply for Social Security disability, you will be asked to complete some initial forms. This is simply information about yourself, names and addresses of your medical providers so they can get your records, and a history of all the types of work you've done in the past fifteen years. If you're applying for SSI, there will also be forms to complete concerning your financial condition, what you own, what income you have, etc.

After a couple of weeks, you will receive more forms to complete, these dealing more specifically with your condition and its impact on your life. For people dealing with CMT symptoms these questionnaires are likely to be concerning fatigue you have and any

pain you may be experiencing. They will also send you forms asking about your daily activities and how you accomplish the routine tasks of daily living. There may be other questionnaires as well based on what they find or don't find in your medical records.

You should spend some time and fill these forms out carefully and completely. Don't leave any blanks; write "N/A" if it doesn't apply to you. When filling them out, comment on your bad days, not the days when you're feeling fine.

It is best if you fill these forms out yourself. The Analyst reviewing the form will look at how you filled it out as well as what you say. Don't worry if you have to make corrections or changes. Just line them out and re-write it. You won't be graded on neatness, but make sure you print clearly enough so that it can be read. Use blue or black ink when completing the forms. You can also put information on additional sheets of paper if there's not enough room on the form, but be sure to clearly label the answer and make sure your name and Social Security number is on each sheet.

If you use a computer or typewriter or have someone fill it out for you because you are unable to write legibly, explain that on the form and tell why. If the form was especially difficult for you to complete, also explain that and include how long it took you to fill it out. Everything will be considered when reviewing your claim.

No one can guarantee your claim for benefits will be approved, but with preparation, thorough and complete medical records, and a focusing on functional symptoms, your claim will have a better chance of being approved.

Additional information about Social Security benefits is available from the Social Security Administration at 1-800-772-1213 or at www.ssa.gov. Another source of information is the Social Security

Administration Disability Programs Office of Public Inquiries at 1-800-772-1213 (same as above) or www.socialsecurity.gov/disabilities.

Organizations, Discussion Forums, and other Resources

The final source of help and information for patients and families dealing with CMT (and some would say- the most important) are the organizations and groups that provide support and information on living with the disorder.

A list of the most useful sites is compiled below:

The Charcot-Marie-Tooth Association
2700 Chestnut Street
Chester, PA 19013
1-800-606-2682
www.charcot-marie-tooth.org or www.cmtinfo.org or
(Founded in 1983, this organization publishes a newsletter six times a year, hosts patient/family conferences, funds numerous CMT research grants, and has published books and pamphlets about the disorder and how to deal with it.)

Charcot-Marie-Tooth Association Australia, Inc
www.e-bility.com/cmtaa

CMT Family Support
http://health.groups.yahoo.com/group/CMT_Family_Support
(Info, articles and a discussion forum)

CMT United Kingdom
www.cmt.org.uk
(A new and useful information source from England)

CMTUS
Http://health.groups.yahoo.com/group/CMTUS
(Information, research articles and a discussion forum)

Hereditary Neuropathy Foundation
www.hnf-cure.org
(CMT information and discussion forums)

Hereditary Neuropathy with Liability to Pressure Palsies (HNPP)
www.hnpp.org
(Information and resources related to HNPP)

Muscular Dystrophy Association
1-800-572-1717
www.mda.org
(CMT is one of the MDA's forty diseases. See the section on MDA for detailed information.)

Additional resources, which are not reproduced here because the listings are updated frequently, may be found on the Resources page of the CMTA website at http://www.charcot-marie-tooth.org/resources.php. These include state-by-state lists of physicians familiar with CMT, support groups, and other agencies and organizations that provide information and assistance.

Conclusion

No one should be forced to face the uncertainties of a progressive disorder without help. Until science discovers the secret to correcting the genetic alterations that cause CMT, help in living day to day with the disorder is crucial. The organizations, agencies and information provided here will help the newly diagnosed person unravel some of the mysteries of dealing with CMT.

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Charcot-Marie-Tooth Association
2700 Chestnut Street
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Tel: 800-606-2682
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www.charcot-marie-tooth.org
info@charcot-marie-tooth.org

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