CHARCOT-MARIE-TOOTH DISEASE: GENETIC AND REHABILITATION ASPECTS

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Abstract. Charcot-Marie-Tooth hereditary motor and sensory neuropathy refers to a group of disorders characterized by a chronic motor and sensory polyneuropathy. Typical cases have distal muscle weakness and peroneal atrophy often associated with mild to moderate sensory loss, depressed tendon reflexes, and pes cavus. Hereditary neuropathies are categorized by mode of inheritance and chromosomal locus. The diagnosis is based on family history, characteristic findings on physical examination, EMG, nerve conduction velocity testing, and occasionally on nerve biopsy. The disorder shows allelic and non-allelic genetic heterogeneity, thus mutations of different genes leading to the same clinical features. Also, different mutations of the same gene may lead to different phenotypes. Molecular genetic testing is available in clinical laboratories for diagnosis of 7 subtypes of the disease. Genetic counseling and risk assessment depend on the inheritance. We present two cases with Charcot-Marie-Tooth type 1 and type 2 respectively. There is no cure for the disorder, although physical therapy and moderate activity are often recommended to maintain muscle strength and endurance.

Keywords: hereditary neuropathy, genetic heterogeneity, rehabilitation

INTRODUCTION

Charcot-Marie-Tooth disease (CMT) is one of the most common inherited neurological disorders, estimated to affect about 1 in 2,500 individuals [3]. CMT, also known as hereditary motor and sensory neuropathy (HMSN) or peroneal muscular atrophy, comprises a group of disorders that affect peripheral nerves with chronic motor and sensory polyneuropathy [12]. It describes the group of inherited neurological disorders characterized by slowly progressive degeneration of the muscles in the foot, lower leg, hand, and forearm, and mild loss of sensation in the limbs, fingers, and toes [4, 11]. The disease is often misdiagnosed, although is one of the most common inherited neuromuscular disorders. The symptoms depend on which form of the disease is inherited, but generally start between mid-childhood and early adulthood [2]. The first signs are usually foot abnormalities, such as an unusually high arch or flexed toes. Typical cases have distal muscle weakness and peroneal atrophy often associated with mild to moderate sensory loss, depressed tendon reflexes, and pes cavus [1, 6]. Sprained ankles and fractures of the ankles and lower legs may also occur. As the disease progresses muscle weakness and wasting leads to difficulties with walking, running and balance. If the hands are affected, daily activities can become difficult. CMT is not a fatal disease and the disorder does not affect normal life expectancy [13].

Hereditary neuropathies are categorized by mode of inheritance and chromosomal locus. There are many forms of CMT disease [5, 6, 23]. The diagnosis is based on family history, characteristic findings on physical examination, EMG, nerve conduction velocity testing, and occasionally on nerve biopsy. The main forms include CMT1, CMT2, CMT3, CMT4, and CMTX [5, 8].

CMT1 is the most frequent and results from abnormalities in the myelin sheath. There are three main types: CMT1A is an autosomal dominant disease resulting from a duplication of the gene on chromosome 17 that carries the instructions for producing the peripheral myelin protein-22 (PMP-22). The PMP-22 protein is a critical component of the myelin sheath. An overabundance of this gene causes the structure and function of the myelin sheath to be abnormal [11, 13].

CMT is caused by mutations in genes that produce proteins involved in the structure and function of either the peripheral nerve axon or the myelin sheath. Although different proteins are abnormal in different forms of CMT disease, all of the mutations affect the normal function of the peripheral nerves. Consequently, these nerves slowly degenerate and lose the ability to communicate with their distant targets [21]. The degeneration of motor nerves results in muscle weakness and atrophy in the extremities (arms, legs, hands, or feet), and in some cases the degeneration of sensory nerves results in a reduced ability to feel heat, cold, and pain [1, 6]. There is no cure for CMT, but physical therapy, occupational therapy, braces and other orthopedic devices, and even orthopedic surgery can help patients cope with the disabling symptoms of the disease. In addition, pain-killing drugs can be prescribed for patients who have severe pain [8, 9, 10].

Physical and occupational therapy, the preferred treatment for CMT, involves muscle strength training, muscle and ligament stretching, stamina training, and moderate aerobic exercise. Most therapists recommend a specialized treatment program designed with the approval of the patient's physician to fit individual abilities and needs [18]. Therapists also suggest entering into a treatment program early; muscle strengthening may delay or reduce muscle atrophy, so strength training is most useful if it begins before nerve degeneration and muscle weakness progress to the point of disability [8, 16, 20].

Stretching may prevent or reduce joint deformities that result from uneven muscle pull on bones. Exercises to help build stamina or increase endurance will help prevent the fatigue that results from performing everyday activities that require strength and mobility [17]. Moderate aerobic activity can help to maintain cardiovascular fitness and overall health.

Most therapists recommend low-impact or no-impact exercises, such as biking or swimming, rather than activities such as walking or jogging, which may put stress on fragile muscles and joints. Some CMT patients may decide to have orthopedic surgery to reverse foot and joint deformities [15].

MATERIALS AND METHODS

We present two cases with Charcot-Marie-Tooth type 1 and type 2 respectively. The diagnosis was established on the basis of the family history, clinical examination, neurological examination, EMG and NCV. A comprehensive family history is needed as it helps not only establishing the diagnosis, but also the inheritance of the disorder. A three-generation family history with attention to other relatives with neurologic signs and symptoms was obtained. Clinical evaluation in cases without positive familial history for the disease is necessary to exclude other possible causes of the neuropathies [1].

Molecular tests are also performed if they are available. These tests may find out mutations of different genes from different chromosomes, but the clinical picture may reveal overlapping of clinical features of different clinical forms. Mutations may be detected using molecular techniques, such as:

- FISH method
- PCR based methods
- DNA sequencing

RESULTS AND DISCUSSIONS

Proband C. N., 29 year-old had unilateral equinovarus and pes cavus, in the left side. The symptoms began at about 10 years. He did not have sensorial involvement. Nerve conduction velocity is reduced in both legs, in the left leg being only 28m/s. The proband's father, aged 64, has a mild bilateral peroneal atrophy. The same symptoms are present in two uncles of the proband, but they have a more severe involvement. The proband is married and he asked for genetic counseling to find the risk for his descendents to be affected. The family history also reveals that the proband's brother is healthy. The study of the family tree reveals that the disease is present in three generations in this family, which suggests a dominant inheritance. The clinical aspects, as well as the reduced nerve conduction velocity plead for the diagnosis of Charcot-Marie-Tooth type I. Molecular analysis performed at Human Genetics Institute Erlangen, Germany confirm the existence of a duplication 17p11.2-12. Thus, it was established that the inheritance is autosomal dominant and the reccurence risk is 50% for the descendents.

The second case, proband P. L., aged 41 had bilateral equinovarus and pes cavus. The onset was 6 years ago. The subject did not have sensorial involvement. Nerve conduction velocity was within the normal values. The proband's mother, aged 64, also has bilateral pes cavus, bilateral peroneal atrophy and hypoacusis. The same symptoms are present in her brother, the proband's uncle. The proband is married and she has two children, a boy and a girl, both unaffected. The family history also reveals that the proband's sister is unaffected. The clinical features, the normal NCV plead for the diagnosis of Charcot-Marie-Tooth type 2.

The evaluation strategy of Charcot-Marie-Tooth hereditary neuropathy for a given individual involves a medical history, physical examination, neurologic examination, and nerve conduction and EMG testing, as well as a detailed family history and the use of molecular genetic testing when available.

The disorder shows allelic and non-allelic genetic heterogeneity, thus mutations of different genes may lead to the same clinical features. Also, different mutations of the same gene may lead to different phenotypes. Molecular genetic testing is available in clinical laboratories for diagnosis of 7 subtypes of the disease. Genetic counseling and risk assessment depend on the inheritance.

CMT1 is characterized by distal muscle weakness and atrophy, sensory loss, and slow nerve conduction velocity (typically 5-30 meters per second; normal: >40-45 m/s). It is usually slowly progressive and often associated with pes cavus foot deformity and bilateral foot drop. Affected individuals usually become symptomatic between ages five and 25 years. Fewer than 5% of individuals become wheelchair dependent. Life span is not shortened.

CMT2 is an axonal peripheral neuropathy characterized by distal muscle weakness and atrophy. Nerve conduction velocities are usually within the normal range; however, occasionally they fall in the low-normal or mildly abnormal range (35-48 m/s). Peripheral nerves are not enlarged or hypertrophic. CMT2 shows extensive clinical overlap with CMT1; however, in general, individuals with CMT2 tend to be less disabled and have less sensory loss than individuals with CMT1. A threshold of 38 m/s for median motor nerve conduction is often used clinically to distinguish CMT1 from CMT2.

Individuals with CMT may have a negative family history for many reasons, such as mild subclinical expression in other family members, autosomal recessive inheritance, or a de novo (new) mutation for a dominant gene. It is estimated that about one-third of individuals with identifiable point mutations in PMP 22, GJB 1, or MPZ causing the CMT hereditary neuropathy phenotype have de novo mutations, and thus present as simplex cases [4]. PMP22 duplications, which are much more common than point mutations, occur as de novo mutations in about 10%-20% of people with CMT1. In more than 90% of individuals with a CMT1 phenotype a mutation is found in one of three genes (PMP 22dup, MPZ, GJB 1).

Rare mutations in other genes and point mutations in PMP22 are rare causes of the CMT phenotype. When tests for the more common forms of CMT are negative, the physician must decide if searching for rarer types of CMT justifies the cost. Prognosis and genetic counseling are frequent reasons for considering such testing.

Genetic counseling is the process of providing individuals and families with information on the

nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. Genetic risk assessment depends on the inheritance of the disorder. Charcot-Marie-Tooth may be transmitted in an autosomal dominant, autosomal recessive, or X-linked dominant manner depending on the genetic subtype in a family.

One study found that many individuals with CMT give themselves high disability ratings and 36% would choose not to have children [18]. It is appropriate to offer genetic counseling, including discussion of potential risks to offspring and reproductive options, to young adults who are affected or at risk.

Prenatal diagnosis for pregnancies at increased risk for some types of CMT is possible by analysis of DNA extracted from cells obtained by chorionic villus sampling at about ten to 12 weeks' gestation or amniocentesis usually performed at about 15-18 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed. Requests for prenatal diagnosis of adult-onset diseases are uncommon. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate [2].

There is no cure for the disorder, although physical therapy and moderate activity are often recommended to maintain muscle strength and endurance. Treatment is symptomatic. Affected individuals are often evaluated and managed by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists [6, 9]. Quality of life has been measured and compared among various groups of individuals with Charcot-Marie-Tooth (CMT) [22]. Orthopedic surgery may be required to correct severe pes cavus deformity [10]. Surgery is sometimes required for hip dysplasia [8]. Exercise is encouraged within the individual's capability and many individuals remain physically active.

The cause of any pain should be identified as accurately as possible [9, 16]. Daily heel cord stretching exercises to prevent Achilles' tendon shortening are desirable, as well as gripping exercises for hand weakness [22].

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