Otorhinolaryngology Clinical Features of Charcot-Marie-Tooth Disease

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SUMMARY

Introduction: Charcot-Marie-Tooth disease is the most common hereditary peripheral neuropathy in humans, presenting incidence of 1: 2500 people.

Objective: Review the literature about aspects of Charcot-Marie-Tooth disease, with emphasis on otolaryngologycal clinical features.

Method: It was used as methodology consults the on line data bases such as Cochrane, LILACS, MEDLINE, OMIM e SciELO, applying the research the terms Charcot Marie Tooth disease, Hereditary Motor and Sensory Neuropathy Type I and Hereditary Motor and Sensory-Neuropathy Type II, to article published between years 1997 and 2007.

Literature's review: Clinical features on Charcot-Marie-Tooth disease normally begin between first and second life decade, varying accordingly with disease type, 1 or 2, and the linked genetic mutation. Classic clinical symptoms are characterized as bilateral and symmetrically progressive debility of distal muscles of extremities, mostly legs and feet, leading to a change of walking. It may cause sensorineural hearing loss. Vocal changes are not common.

Final Considerations: Several aspects of Charcot-Marie-Tooth disease still continue obscure, being the otolaryngological changes are few investigated, rending difficult a premature and suitable diagnosis and treatment of this changes.

Key words: Charcot-Marie-Tooth disease, hereditary motor and sensory neuropathy type I, hereditary motor and sensory-neuropathy type II, HMSN type I, HMSN type II.

Introduction

Charcot-Marie-Tooth Disease (CMT) is the most common type of Hereditary Peripheral Neuropathy (1) in humans, together with Hereditary Motor and Sensory Neuropathy (2), affecting around 1 in 2,500 people (3).

Jean-Marie Charcot, Pierre Marie, and Howard Henry Tooth discovered CMT in the 19th century and it was also known as "peroneal fibular muscular atrophy" (4).

CMT affects children and adults and is inherited as an autosomal dominant trait, characterized by a progressive weakness and wasting of distal muscles, loss of leg muscle reflexes, sometimes involving arm's and reduction of distal sensibility (2,5). The severity degree depends on genetic basis of patients (2).

Its classification is always under revisions and nowadays it is divided into two electrophysiological-criterion-based groups: type 1 (demyelinating) and type 2 (axonal).

CMT1 is established by the reduction on nervous stimuli conduction velocity and nerve hypertrophy, while CMT2 conduction velocity is normal but there is axonal neuropathy (4).

The motivation for researching Charcot-Marie-tooth Disease was the observation of a daily interdisciplinary performance at the *Hospital Universitário Bettina Ferro de Souza - Universidade Federal do Pará* and *Universidade do Estado do Pará* (University Hospital – Federal University and State University) involving fields as Otorhinolaryngology, Neurology, Pediatrics, Psychology, Social Service Care and Physiology, mainly when concerning assistance to patients with special needs. The reason to carry such study is to make health professionals aware of such syndrome. Although not common, it holds serious consequences for people, especially when late diagnosed.

Objective

To review the literature on different aspects of Charcot-Marie-Tooth Disease, with emphasis on ENT clinical symptoms.

Method

On-Line search of data basis provided the necessary information and articles to accomplish this revision. They can be accessed at any time to be searched and updated accordingly to scientific literature output.

A list of data basis which was searched follows: Cochrane, LILACS, MEDLINE, OMIM and Scielo, applying to the research the terms Charcot Marie Tooth Disease, Hereditary Motor and Sensory Neuropathy Type I and Hereditary Motor and Sensory-Neuropathy Type II, for articles published between 1997 and 2007.

Literature Review

CMT predominance

CMT is the most common genetic neuropathy accounting for 80 to 90% of cases (5). Occurrences of all CMT types range from 20 to 40 in 100,000 people worldwide (6). In Italy there were 10.8 occurrences in 100,000 people; in Japan the number was 17.5 in 100,000 people (7), and in the U.S.A. it was 42:100,000 people (5).

Clinical symptoms

CMT symptoms begin between the first and second decade of life (4), but it may vary according to types, CMT1 or CMT2, and genetic mutation associated to them (2). CMT1 is more common and often appears 10 years earlier than CMT2 (8).

Classic clinical symptoms are characterized by bilateral and symmetrical progressive debility of distal muscles, mainly legs and feet, leading to a change on walking (4,9,10). As disease progresses, there is motor and sensory loss and then loss of reflexes (7). Such sensory and motor loss causes bone abnormalities such as high arch foot (11,12), shortening of the calcaneous tendon (7,12), curled toes, reduced angle of foot dorsiflexion (12,13) and kyphoscoliosis (11), and others, leading to difficulties in walking (4,8).

Comparing CMT1 and CMT2, it was observed differences on clinical symptom prevalence in both. Foot weakness and deformities and lower velocity of nervous stimuli conduction arise from CMT1 (14).

Disease evolution depends on clinical conditions. Patients with CMT2 present slower and less severe evolution (6,14,16), symptom predominance on inferior members and rare involvement of superior ones (15). Nevertheless, due to uncommon gene mutations in some cases, CMT2 progresses quicker and more severely, as well as uncommon

symptoms such as vocal changes and diaphragm paralysis (17,18).

Age can also be a sign of evolution and prognosis of the disease. In both CMT1 and CMT2, their early start seems to be connected to evolution and prognosis of the disease (16,17). Patients who present severe clinical symptoms are likely to be developed early CMT1. A study on patients who developed the disease before 20 years old showed that the conduction velocity of motor stimulus on the median nerve was lower, leading to a higher functional dysfunction than the patients who developed the disease later (17).

Otorhinolaryngological symptoms

Auditory Alterations on CMT

Auditory alterations caused by CMT are common (19,20), although the number of patients who are affected is uncertain (19). They present sensorineural hearing loss (20,21), in which a cochlear part can be found, but there is no common sense towards it (22,23). A study of the year 2002 showed the two parts on audiological involvement in the studied patients (24).

There was a hypothesis that hearing loss is caused by the involvement of the 8th pair of cranial nerve (20). Such hypothesis is in accordance with hearing loss due to cochlear nerve dysfunction as part of general neuropathy caused by the disease found in three patients from a gypsy family affected with CMT (20).

CMT-induced hearing loss is clinically different from general disorders found in patients with CMT. It presents good results with cochlear implantation for patients with auditory neuropathy (25).

Hearing loss by CMT is associated with mutations on PMP22, MPZ and Cx-32 genes (20,26,27,28,29). Nevertheless, mutation neither on Cx-32 nor on PMP22 genes determines deafness, as not all patients who present such mutations are deaf (20,27). Several studies show the association among some kind of mutation, transport and elimination of aminoacid on PMP22 gene with CMT (2,26,30).

Vocal Alterations on CMT

CMT presents several phenotype distinctions which are described in the literature, though genetic mutations that cause vocal alterations are not common. Vocal cords paresis might be associated to a more severe variable of the disease (18). It can also occur bilateral vocal cords paresis, although it is usually caused by diseases that affect central nervous system at first, such as hydrocephaly, Chiari malformation and meningomyelocele (5).

Genetic vocal alterations might be associated to mutation on GPAP1, Q163X, S194X, PMP22 and EGR2 genes, although information on that is non-conclusive or conflicting, and occurrences are rare (18).

Diagnosis

In order to firstly suppose CMT, it is necessary to know patient's family background. If there is a previous background, then it is simple to assure CMT; however, patients from small families might represent sporadic cases. Important clue for CMT is long-term background of foot abnormalities such as high arch foot and others since childhood (2).

Regarding patient's background, it is important to know about signs of motor development, presence of cramps, difficulties in walking or running, shoe changes due to foot abnormality, presence of callosity and difficulty in moving toes (12).

Electrophysical and histopathological studies are necessary to diagnose and distinguish types of CMT (1 or 2) (3). CMT1 is diagnosed when there is reduction on motor stimulus conduction velocity by median nerve (3), and it is usually lower than 38m/s (2,31). Yet, CMT2 does not present reduction on that velocity, but an axonal neuropathy (6). Histopathological findings of biopsies of peripheral nerve on CMT1 present areas of alternated demyelination and remyelination, and also onion-bulb-like structures (3), which are not found in CMT2, but a chronic axonal atrophy (17).

Diagnosis by nuclear magnetic resonance imaging and CT scan are useful for detecting and characterizing pathological condition of skeletal muscles. In CMT1, it might occur presence of peroneus muscles and fat infiltration in them (12), and also cranial nerve thickening, although being rare (32).

After patient is clinically, neurophysically and in some cases histopathologically classified, molecular diagnosis should be performed in order to classify the type of disease (CMT1 or CMT2), the inheritance condition (autosonal dominant, autosomal recessive or X-linked) and if necessary the genetic mutation that caused disease (2,23).

Therapy

There is no therapy for CMT1, but ascorbic acid has been efficient when tested in mice. There are studies in the

3rd stage of randomization with such drug in patients with CMT1 (34). Several devices have been tested in order to evaluate these patients' rehabilitation (35).

Expressive reversion of peripheral muscle fatigue by making use of modafinil has been under observation (36). Other studies have been carried to observe neuromuscular response from patients with CMT, as for example, with the use of mivacurium drug (37).

Deaf patients presented good results through cochlear implantation (25).

Final Considerations

Charcot-Marie-Tooth disease is the main genetic neuropathy (2). There is still a lot to discover about it, as genetic researches are at their start. Several genetic alterations are involved in this process, by leading to different clinical evolutions that characterize its polymorphism (38) with severe symptoms (2,4,7,16,17). The more knowledge on these alterations, the better will be therapy and improvement of prognosis of patients with CMT.

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