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Charcot–Marie–Tooth disease: Genetics, epidemiology and complications

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ABSTRACT

Background and aims: Charcot Marie Tooth disease (CMT) is the most prevalent hereditary neuropathy and its frequency is 1 in 2500. CMT is a heterogeneous disease and has different clinical symptoms. The prevalence of CMT and involved genes differ in different countries. CMT patients experience considerable sleep problems and a higher risk of decreased quality of life. In this work it was aimed to provide a review on the genetic and epidemiologic aspects of this disease.

Methods: In the current review article, we performed a literature search on the epidemiology of Charcot–Marie–Tooth disease" and provided a brief review on epidemiology, genetic, and complications of CMT. Databases Web of Science and PubMed were searched using the Endnote software for the publications on CMT during 2000 to 2016.

Results: Charcot Marie Tooth disease has different prevalence around the world and is the most common neuropathy. Epidemiological studies have estimated the prevalence of CMT in Japan 1/9200, in Iceland 1/8300, in Spain 1/3500 and in Italy 1/5700.The patients have different phenotype and the age of onset. There is a variety of inherited patterns of disease and many genes have been identified responsible whose mutations are main cause of the disease.

Conclusion: Due to the impact of this kind of disabilities on the national health, further studies seem to be necessary to gain better knowledge of the disease particularly in the regions with higher prevalence. Moreover molecular biology services offered by genetic laboratories can reduce the incidence of disorder.

Keywords: Charcot Marie Tooth, Neuropathy, Electrophysiology, Epidemiology.

Review article

INTRODUCTION

The peroneal muscular atrophy was described about 120 years ago by Charcot, Marie and Tooth in Paris and England, respectively. The described disorder was a familial and neurological disease. It was called CMT, to respect Charcot, Marie and

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Tooth who described it for the first time. Charcot Marie Tooth disease (CMT) is the most prevalent hereditary neuropathy and its frequency is 1 in 2500. The other name of CMT disease is hereditary motor and sensory neuropathy(HMSN).[1,2] Because of involving more than 80 genes in CMT, it is a heterogeneous group of inherited peripheral neuropathies.[3,4] Based on electrophysiological index, CMT is subdivided into two major forms: demyelinating and axonal. In the demyelinating type, motor nerve conduction velocity (MNCV) is under 38 m/s whereas in axonal forms, MNCV is normal (above 38 m/s), but axons are affected. In the intermediate type of this disorder, intermediate MNCV about 25-45 m/s and/or heterogeneous clinical manifestation is common.[5] The CMT disease has different inheritance pattern (including Autosomal Recessive(AR), Autosomal Dominant(AD), X-linked, and mitochondrial). In addition, the onset of CMT can be in different ages and clinical features varies in patients.[6] Despite a high number of publications providing comprehensive and detailed information on CMT, there is little about the epidemiology of this disease. In this work, it was aimed to provide a concise review on the genetic and epidemiologic aspects of this disease. Databases Web of Science and PubMed were searched using the Endnote software for the publications on CMT during 2000 to 2016.

From the genetic perspective, Charcot Marie Tooth is a heterogeneous disease, but the clinical phenotype and manifestation is homogeneous and similar. This similar phenotype includes the weakness of distal limb muscles) especially the peroneal compartment of leg), loss of sensation in the distal extremities, skeletal abnormalities and reduction or lack of reflexes in deep tendons.[7] Triad flaccid paresis, atrophy, and decreased or loss of reflexes are outcomes of the lower motor neuron damage. The severity of the disease ranges over a wide spectrum. Age of onset is different among the patients, ranging from a floppy infant to an elderly man with slowly progressive peripheral neuropathy.[8] The classic clinical picture of Charcot Marie Tooth disease is pescavus, hammertoes, atrophy in muscles, weakness in the distal compartment of the legs, lack of vibratory sensation, absent of touch sensation and loss of reflexes in Achilles tendon.[9,10]

The identification of inheritance pattern is the first step of CMT classification. CMT is inherited via autosomal dominant, autosomal recessive and X-linked patterns. The second step of classification is according to the process of neuropathy disorder in each subset.[10,11] According to electrophysiological standards CMT is usually divided into two classes; demyelinating and axonal forms (CMT1 and CMT2 respectively). In CMT type 1 motor nerve conduction velocities (MNCV) is less than 38 m/s and the effect of demyelination and remyelination in nerves can be seen in sural nerve biopsy. In CMT type 2 motor nerve conduction velocities is somewhat decrease or even normal[12]. CMT4 is Autosomal recessive and CMTX is not dependent to the Nerve Conduction Velocity.

To determine the subtypes in CMT disease, the mutant gene should be distinguished. It is known that more than 40 genes can cause CMT.[13] Among CMT subtypes, duplication in PMP22 geneis cause of the most common form of the disease, CMT1A. This subtype contains 70-80% of the CMT1 (demyelinating)cases.[14] The subtype CMT2 manifested by MPZ mutations is involved in 10–30% of the CMT cases.[15] Furthermore, GJB1 and GDAP1 mutations lead to CMTX1 and CMT4A respectively.

The clinical features are sometimes uncommon for CMT type 2, CMT type 4, and CMTX. For instance, CMT4 is recessive with early onset and severe symptoms.[14] The cause of demyelinating form of CMT with Autosomal Dominant inheritance pattern (CMT type 1A) is usually PMP22

gene-duplication (on 17p11.2 locus) and it is almost 20% of all CMT cases with neuromuscular problems and a chronic peripheral neuropathy. Other causes for CMT1 (demyelinating) include mutations in P0 (1q22), LITAF (16p13) and EGR2 (10q21) genes.[16] Table 1 and Table 2 summarize the main types of CMT together with the responsible gene and their chromosomal locus.

Table 1: The most common subtypes of CMT disease and the involved genes

CMT subtype	Mutation
CMT1A	PMP22 duplication
CMT2A2	MFN2
CMTX1	GJB1
CMT4A	GDAP1

Table 2: The chromosomal locus for the most prevalent types of CMT1

The mutant gene	Locus
PMP22	17p11.2
P0	1q22
LITAF	16p13
EGR2	10q21

Charcot Marie Tooth is a chronic disease and has an unpleasant effect on condition of patient's life. The undesirable effect impact different part of life, including mental and physical aspects.[9]

In CMT, disturbed sleep and respiratory system dysfunction may also be seen, which include the following items: obstructive apnea in sleep, streaked legs syndrome, vocal cord disorder, laryngeal neuron dysfunction and respiratory system impairment.[17]

In Germany, a large study was conducted on 200 patients with Charcot Marie Tooth[13] wherein, patients complained about fatigue, lack of good sleep and feeling sleepy during the day hours. Other symptoms including dysphagia, dyspnea and obstructive apnea in sleep was described in another report.[18]

Due to the lack of specific recommendations for the respiratory and sleep disorders, individuals need long-term care. Moreover, there are limitations for treatment of CMT patients during illness. Some reports show that during the pregnancy, patient's signs and symptoms become worse.[19] In case of surgery, regional anesthesia is a good alternative to anesthesize rather than general anesthesia during pregnancy.[19]

CMT has been shown to increase the risk for complications during delivery, specifically abnormal birth presentation, post-partum bleed, and with higher rates of emergency interventions during delivery.[20] Many medications can cause patient's condition worse. For example, progesterone antagonists that are prescribed for treatment of CMT patients lead to abnormal baby born, dystocia and bleeding. Additionally, chemotherapy drugs like vinca alkaloids and taxol that target cell microtubules causing them depolymerized, lead to worsening CMT.[21] It seems that these drugs cause disruption of axonal transportation and thus worsen or accelerate the development of new neuropathy. Chemotherapy drugs are not the only risk factors for the Charcot Marie Tooth disease, there is a large list of interventional medications prepared by the CMT Association which is regularly updated.[22]

In all epidemiological studies, the important issue is whether the results can be generalize or not, and this depends on the population chosen for the study. In clinical trials, there is a non-partisan data collection, because the members elected in a clinical population and large families and patients with severe disabilities also participated in the study.[23] However, sporadic cases are

important because it shows disease with autosomal recessive inheritance pattern or a de-novo mutation. There are some items that can increase or decrease the estimation of disease prevalence. For example, misclassification of sporadic and familial non-CMT cases can increase the estimation and the CMT patients who do not participate in the study can reduce the estimation (eg, CMT2 has late onset and the person is a carrier of the disease but does not participate in the study).[24] Epidemiological studies have estimated the prevalence of CMT in Japan1/9200, in Iceland1/8300, in Spain 1/3500 and in Italy 1/5700.The difference in rates is mainly due to different methods used to determine and diagnose disease and sometimes because of human ethnicity and unequal distribution of point mutations in the world and dominance of founder effect in some areas. Clinical studies conducted that CMT1 outbreak is more than CMT2 and only one exception is in Japan, which founder effect occurred for MPZ gene (Thr124Met).[25] In a study conducted by G. J. Braathen1 in Akershus (the East Norway County), it was estimated that 13.6% of the families carry the PMP22 gene duplication while CX32 mutation was estimated to be about 6.2%. Moreover, MFN2 mutation and MPZ mutation were estimated around 6.2% and 4.8%, respectively.[26] The prevalence of duplication/deletion of PMP22 and MFN2 point mutation in the general population was less than clinical population, while for point mutation in CX32 the similar prevalence in both populations was estimated.[14,27-29]

DISCUSSION

CMT is a heterogeneous disease and has different pattern of inheritance, different age of onset and different clinical symptoms. The outbreak and involved genes vary in different countries. Identifying common mutations in each region in the world can help to identify the involved proteins and it is good for correct diagnosis of the disease and may be entered in the world of treatment. Unfortunately, epidemiological studies on CMT have not been yet conducted in Iran. Hopefully, the researches currently conducted by our group could identify affected individuals and families. This information together with our molecular genetic testing will further be of benefit to the patients and their families and will prevent from affected child birth.

CONCLUSION

Due to the impact of this kind of disabilities on the national health, further studies seem to be necessary to gain better knowledge of the disease particularly in the regions with higher prevalence. Moreover molecular biology services offered by genetic laboratories can reduce the incidence of disorder.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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