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Research Article

Genetic and clinical spectrum of Charcot-Marie-Tooth disease in Turkey

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Abstract

Objective: Charcot-Marie-Tooth (CMT) disease is one of the most common inherited diseases of the peripheral nervous system. Over the past two decades, there have been rapid advances in understanding the molecular basis of CMT with more than 100 causal genes detected. Due to genotypic and phenotypic heterogeneity, disease course is variable. This study aims to evaluate CMT patients clinically and genetically.

Method: The files of the cases diagnosed with CMT and followed up in the our horpital were scanned. The clinical and genetic information of the patients included in the study was recorded in the forms prepared within the scope of the study. Clinical and genetic information of patients were evaluated.

Results: 19 patients diagnosed with Charcot-Marie-Tooth who met our study criteria were included in the study. Of our patients, 10 (52.6%) were girls and 9 (47.4%) were boys. The age of our patients was between 108 and 216 months, average 160 months. The initial complaint in 16 (%84,2) patients was walking disorder and it was the most common complaint. Two patients (10.5%) had poor head retention, 1 patient (5.3%) had respiratory distress, one patient (5.3%) had dropped foot, and one patient (5.3%) had low back pain. The mutation in the PMP22 gene detected in 8' (42.1%) of 19 patients. SH3TC2 gene, mutation was found in 3 (15.8%) of the patients and GDAP1 gene was found in 2 (%10.5) of the patients.

Conclusion: It is very important to diagnose diseases that cause socioeconomic disadvantage, such as CMT disease, early. Suggestions and activities to reduce consanguineous marriages are very valuable for our country in reducing the prevalence of this disease and similar diseases. The fact that there are very few studies on CMT disease in our country suggests that the significance and value of our study increases.

Key Words: charcot-marie-tooth; neuropathy; hereditary; genetics

Introduction

Charcot-Marie-Tooth disease (CMT), also known as hereditary motor and sensory neuropathy, is the most common inherited peripheral neuropathy, affecting approximately 1 in 2,500 individuals worldwide [1]. It is characterized by progressive degeneration of peripheral motor and sensory nerves, resulting in distal muscle weakness, sensory loss, foot deformities, and gait impairment. Although CMT is not life-threatening, it causes considerable functional disability, particularly in children with early disease onset.

CMT is both clinically and genetically heterogeneous, with more than 100 disease-causing genes identified to date [2]. Based on electrophysiological findings, it is classified into demyelinating, axonal, and intermediate forms. Among these, *PMP22* is the most frequently implicated gene, accounting for nearly half of all CMT cases. Other genes, including *SH3TC2*, *GDAP1*, *MPZ*, and *MFN2*, are associated with variable clinical phenotypes and disease severity [3-5]. The distribution of these mutations differs across populations, particularly in regions with high rates of consanguineous marriage.

Children with CMT commonly present with delayed motor milestones, gait abnormalities, distal muscle weakness, foot deformities, and reduced deep tendon reflexes [1]. Because of the marked clinical variability and slowly progressive course, diagnosis is often delayed despite advances in electrophysiological and molecular genetic testing. A better understanding of genotype-phenotype relationships is essential for improving diagnosis, prognosis, genetic counseling, and clinical management.

The aim of this study was to evaluate the demographic, clinical, electrophysiological, and genetic characteristics of pediatric patients with CMT followed at a tertiary referral center and to compare patients with

PMP22 mutations with those carrying other pathogenic variants in order to identify potential genotype–phenotype associations.

Materials and methods

Study Design and Patients

This retrospective, single-center study included pediatric patients diagnosed with CMT who were followed at the our hospitale. Patients with a clinical diagnosis of CMT confirmed by electrophysiological and molecular genetic analyses between the study period were eligible for inclusion. A total of 19 patients who met the inclusion criteria were enrolled. Patients with incomplete clinical or genetic data were excluded from the study.

Data Collection

Demographic and clinical data were obtained retrospectively from hospital medical records. The collected variables included age, sex, parental consanguinity, family history of CMT, age at symptom onset, age at diagnosis, age at independent walking, presenting symptoms, neurological examination findings, and ambulatory status. Physical examination findings included the presence of scoliosis, foot deformity, muscle atrophy, sensory impairment, deep tendon reflexes (DTRs), and optic atrophy. Hearing loss was also evaluated.

Electrophysiological and Genetic Evaluation

All patients underwent nerve conduction studies as part of the diagnostic work-up. Based on electrophysiological findings, patients were classified as having either demyelinating or axonal polyneuropathy. Molecular genetic analyses were performed using standard diagnostic methods available at the institution, and pathogenic variants were identified according to current diagnostic criteria.

For genotype-phenotype analysis, patients were divided into two groups: those harboring *PMP22* mutations and those carrying pathogenic variants in other CMT-associated genes. Clinical characteristics, neurological findings, electrophysiological features, and ambulatory function were compared between the two groups.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics software (version XX.0; IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation (SD) or median (minimum-maximum), whereas categorical variables are expressed as frequencies and percentages. Comparisons between the P*MP22* and non-*PMP22* groups were performed using appropriate non-parametric tests because of the small sample size. Categorical variables were analyzed using Fisher's exact test. A two-sided p value of <0.05 was considered statistically significant.

Results

A total of 19 pediatric patients with clinically and genetically confirmed CMT were included in the study. The cohort comprised 10 females (52.6%) and 9 males (47.4%). The mean age at evaluation was 160.7 ± 37.5 months. The mean age at symptom onset was 56.4 ± 50.3 months, whereas the mean age at diagnosis was 116.4 ± 51.0 months, indicating a substantial delay between symptom onset and diagnosis. The mean age at independent walking was 21.8 ± 9.0 months. Parental consanguinity was present in 68.4% of patients, and a positive family history was reported in 57.1%. None of the patients had hearing loss (Table 1).

The most common presenting complaint was gait disturbance, observed in 84.2% of patients. Less frequent initial manifestations included inability to hold the head (10.5%), low back pain (10.5%), foot drop (5.3%), and respiratory distress (5.3%).

Neurological examination demonstrated foot deformity in 84.2% of patients and muscle atrophy in 57.9%. Scoliosis was identified in 31.6%, while sensory impairment was present in 15.8%. Deep tendon reflexes were absent in 42.1% and reduced in 36.8% of patients; only 21.1% had normal reflexes. Ten patients (52.6%) were able to walk independently, eight (42.1%) required assistance, and one patient (5.3%) was non-ambulatory.

Electrophysiological evaluation revealed a predominantly demyelinating neuropathy. Demyelinating polyneuropathy was identified in 15 patients (78.9%), whereas four patients (21.1%) exhibited an axonal pattern.

Molecular genetic analysis identified pathogenic variants in nine different genes. *PMP22* mutations were the most common, accounting for 42.1% of all cases. Mutations in *SH3TC2* and *GDAP1* were detected in three (15.8%) and two (10.5%) patients, respectively, while the remaining patients harbored variants in other CMT-associated genes (Figure 1).

A significant difference was observed only in ambulatory function. All patients carrying *PMP22* mutations were able to walk independently, whereas only two patients (18.2%) in the non-*PMP22* group achieved independent ambulation. The remaining patients with non-*PMP22* mutations required walking assistance or were unable to walk independently. This difference was statistically significant (p = 0.001) (Table 2).

Age	160,7 ± 37,5 month (108-216 ay)
Sex (female/male)	10(%52,6) /9 (%47,4)
Consanguinity Yes/No	13(%68,4)/6 (%31,6)
Family history Yes/No	11(%57,1)/8 (%42,9)
Scoliosis Yes/No	6 (%31,6)/13 (%68,4)
Loss of sensation Yes/No	3 (%15,7)/16 (%84,3)
Foot deformity Yes/No	16 (%84,3)/3 (%15,7)
EMG Demyelinating/axonal	15 (%78,9)/4 (%21,1)

Table 1: The demographic findings

Findings		*PMP22*	Other mutations	*P*
Sex	Female	4 (50)	6 (54,5)	
	Male	4 (50)	5 (45,5)	>0,999
Consanguinity	Yes	4 (50)	9 (81,8)	
	No	4 (50)	2 (18,2)	>0,999
Family history	Yes	6 (75)	5 (45,5)	
	No	2 (25)	6 (54,5)	>0,999
Scoliosis	Yes	3 (37,5)	3 (50)	
	No	5 (62,5)	8 (61,5)	>0,999
Loss of sensation	Yes	2 (25)	1 (9,1)	
	No	6 (75)	10 (90,9)	>0,999
Foot deformity	Yes	6 (75)	10 (90,9)	
	No	2 (25)	1 (9,1)	>0,999
EMG	Axonal	0	4 (36,4)	
	Demyelinating	8 (100)	7 (63,6)	0,103

Table 2: Comparing patients' findings based on their genetic mutations

Discussion

The present study evaluated the demographic, clinical, electrophysiological, and genetic characteristics of pediatric patients with CMT and investigated genotype-phenotype associations by comparing patients with *PMP22* mutations and those harboring other pathogenic variants. Our findings demonstrated that gait disturbance was the most common presenting symptom, demyelinating neuropathy represented the predominant electrophysiological subtype, and *PMP22* was the most frequently identified causative gene [3]. Furthermore, patients carrying *PMP22* mutations showed significantly better ambulatory function than those with other genetic variants, while no significant differences were observed in other clinical characteristics.

CMT is the most common inherited peripheral neuropathy and is characterized by marked clinical and genetic heterogeneity. Consistent with previous reports, the sex distribution in our cohort was nearly equal, reflecting the predominance of autosomal forms of the disease. A remarkable finding was the high rate of parental consanguinity (68.4%), which may explain the relatively frequent occurrence of autosomal recessive mutations such as *SH3TC2* and *GDAP1*. Similar findings have been reported in studies from Turkey and other regions with high consanguinity rates, highlighting the importance of considering regional genetic characteristics when planning molecular diagnostic strategies and genetic counseling [6,7].

The mean age at symptom onset was approximately 4.7 years, whereas the mean age at diagnosis was nearly 10 years, indicating a substantial diagnostic delay. Similar delays have been reported in previous pediatric studies and are largely attributed to the slowly progressive nature of CMT and the nonspecific presentation of early symptoms [8,9]. Initial manifestations, including gait disturbance and delayed motor milestones, are often misinterpreted as developmental variation or orthopedic disorders. These findings emphasize the importance of early neurological assessment, electrophysiological studies, and molecular genetic testing in children presenting with persistent gait abnormalities or distal muscle weakness.

Consistent with previous pediatric cohorts, gait disturbance was the most common presenting symptom in our study, followed by foot deformity, muscle atrophy, and scoliosis [1]. Foot deformities are well-recognized consequences of chronic distal muscle imbalance caused by progressive denervation, whereas reduced or absent deep tendon reflexes represent characteristic clinical findings of peripheral neuropathy. The high prevalence of these neurological signs supports their value in raising clinical suspicion for hereditary neuropathies during routine examination.

Electrophysiological evaluation revealed that nearly 80% of the patients had demyelinating polyneuropathy, consistent with the predominance of CMT1 reported in the literature [4,10]. Likewise, *PMP22* was the most common pathogenic variant identified in our cohort, followed by *SH3TC2* and *GDAP1*. These findings are in agreement with previous studies from Europe and Turkey, in which *PMP22* has consistently been reported as the leading genetic cause of CMT despite considerable genetic heterogeneity [3,6]. The detection of several recessively inherited mutations further reflects the diverse genetic architecture of CMT in populations with high rates of consanguinity and supports the use of comprehensive next-generation sequencing panels rather than sequential single-gene testing.

The most important finding of the present study was the significant association between *PMP22* mutations and preserved ambulatory function. All patients carrying *PMP22* mutations were able to walk independently, whereas most patients with non-*PMP22* mutations required walking assistance or were unable to ambulate independently. This observation is compatible with the relatively mild and slowly progressive clinical course typically described for CMT1A. However, interpretation of this finding should be cautious because the non-*PMP22* group comprised genetically heterogeneous disorders with varying inheritance patterns and disease severity. In particular, severe phenotypes associated with mutations such as *GDAP1* may have influenced the observed difference in functional outcomes.

Several limitations should be considered when interpreting our findings. First, this was a retrospective study conducted at a single tertiary referral center with a limited number of patients, restricting statistical power and generalizability. Second, the non-*PMP22* group included multiple rare genetic subtypes, limiting genotype-specific comparisons. Finally, longitudinal follow-up data were unavailable, precluding assessment of disease progression and long-term functional outcomes.

Despite these limitations, our study provides valuable data regarding the clinical, electrophysiological, and genetic characteristics of pediatric CMT in a Turkish population. The predominance of *PMP22* mutations and the high frequency of autosomal recessive forms observed in our cohort are consistent with the genetic profile previously reported in Turkey. Moreover, the association between *PMP22* mutations and preserved independent ambulation may contribute to prognostic assessment and clinical counseling. Future multicenter studies including larger and genetically homogeneous patient cohorts are warranted to better define genotype-phenotype correlations and optimize personalized management strategies for children with CMT.

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