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ORIGINAL ARTICLE

The Relationship Between Carpal Tunnel Syndrome and Cardiac Involvement in Patients with Mucopolysaccharidosis

Mukopolisakkaridozlu Hastalarda Karpal Tünel Sendromu ile Kardiyak Tutulumun İlişkisi

[1]Banu Kadıoğlu Yılmaz, [2]Melih Timuçin Doğan, [3]Onur Bulut, [2]Ahmet Sert, [4]Hüseyim Yılmaz

[1]Department of Pediatric Nutrition and Metabolism, Faculty of Medicine, Selçuk University, Konya, Türkiye
[2]Department of Pediatric Cardiology, Faculty of Medicine, Selçuk University, Konya, Türkiye
[3]Department of Neurology, Division of Clinical Neurophysiology, Konya City Hospital, University of Health Sciences, Konya, Türkiye
[4]Department of Pediatric Cardiology, Konya City Hospital, University of Health Sciences, Konya, Türkiye

Correspondence

Banu Kadıoğlu Yılmaz, M.D.
Department of Pediatric Nutrition and Metabolism, Faculty of Medicine, Selçuk University, Konya 42250, Türkiye

E-Mail: banukadioglu@yahoo.com.tr

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ABSTRACT

Background/Aims: Mucopolysaccharidoses (MPSs) are a group of progressive multisystemic diseases, and it is unknown whether there is a relationship between these system involvements. In this study, we aimed to investigate whether there is a relationship between cardiac involvement and carpal tunnel syndrome (CTS) in MPS patients.
Methods: The study was conducted as a cross-sectional study between May 12, 2023, and June 30, 2024. Patients between the ages of 2 and 20 years who were diagnosed with MPS Types I, II, IV A, and VI enzymatically and genetically and who underwent electromyography for CTS screening and transthoracic echocardiography for cardiac involvement were included in the study.
Results: Twenty-six MPS patients were included in the study. The mean age of the patients was 128±58 months. There was cardiac involvement in 21 (80.8%) of the patients. Heart valve involvement was present in 20 (76.9%) patients. Our study found that 14 (53.8%) of our MPS patients had CTS. CTS was present in all patients in the MPS type I, II, and VI groups but not in any MPS type IV A patients. As a result of the statistical analysis, the presence of MPS Type IV A was statistically significantly higher in the group without CTS than in the group with CTS ($p<0.001$). The presence of cardiac involvement, combined involvement of the aortic and mitral valves, and the severity of heart valve involvement were found to be statistically significantly higher in the patient group with CTS than in the patient group without CTS ($p=0.007$, $p=0.005$, $p=0.009$, respectively).
Conclusions: Our study found that CTS was more common in patients with cardiac involvement, especially heart valve involvement. It seems considerable to screen these patients for CTS.

Keywords: Mucopolysaccharidosis, Carpal tunnel syndrome, Heart valve involvement, Cardiac involvement

ÖZ

Giriş/Amaç: Mukopolisakkaridozlar (MPS) progresif, multisistemik tutulumla giden bir hastalık grubudur ve bu sistem tutulumları arasında bir ilişki olup olmadığı bilinmemektedir. Bu çalışmada, MPS hastalarında kardiyak tutulum ile karpal tünel sendromu (KTS) arasında ilişki olup olmadığını araştırmayı amaçladık.
Yöntem: Çalışma, 12 Mayıs 2023 ile 30 Haziran 2024 tarihleri arasında, kesitsel bir çalışma olarak gerçekleştirildi. MPS Tip I, II, IV A ve VI tanısı enzimatik ve genetik olarak konulmuş olan, KTS taraması için elektromiyografi ve kardiyak tutulum açısından transtorasik ekokardiyografi tetkiki yapılan 2-20 yaş arası hastalar çalışmaya alındı.
Bulgular: Çalışmaya 26 MPS hastası dahil edildi. Hastaların yaş ortalamaları 128±58 ay idi. Hastaların 21 (% 80.8)'inde kardiyak tutulum mevcuttu. Kalp kapak tutulumu hastaların 20 (%76.9)'sinde mevcuttu. Çalışmamızda MPS hastalarımızın 14 (%53.8)'ünde KTS olduğunu tespit ettik. KTS, MPS tip I, II ve VI hastalarının tamamında vardı, MPS tip IV A hastalarının ise hiçbirinde yoktu. Yapılan istatistiksel analizler sonucunda, MPS Tip IV A olma durumu KTS olmayan grupta, KTS olan gruba göre istatistiksel olarak anlamlı derecede yüksekti ($p<0.001$). Kardiyak tutulum varlığı, aort ve mitral kapakların birlikte tutulumu ve kalp kapak tutulum şiddeti, KTS olan grupta KTS olmayan gruba göre istatistiksel olarak anlamlı derecede yüksek saptandı (sırasıyla, $p=0.007$, $p=0.005$, $p=0.009$).
Sonuç: Çalışmamızda, kalp kapak tutulumu başta olmak üzere kardiyak tutulumu olan hastalarda KTS'nin daha sık olduğunu bulduk. Bu hastalarda CTS taramasının yapılması önemli görünmektedir.

Anahtar Kelimeler: Mukopolisakkaridoz, Karpal tünel sendromu, Kalp kapak tutulumu, Kardiyak tutulum

Introduction

Mucopolysaccharidoses (MPSs) are a group of inherited metabolic diseases among the lysosomal storage diseases that develop as a result of the accumulation of glycosaminoglycans (GAGs) in various tissues (1). There are seven subtypes with different signs, symptoms, and clinical findings (1). Enzyme replacement therapies (ERT) and hematopoietic stem cell transplantation improve various system involvements in MPS and increase life expectancy (2). With ERT, a decrease in the size of the liver and spleen and a decrease in urinary GAG excretion are observed (3). However, since the impact of ERT on the heart valves, trachea, bronchi, eye, vestibular system, and central nervous system is limited, the progressive involvement in these systems often deteriorates with age (3).

The clinical spectrum of MPS may vary, from fatal

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findings in the intrauterine period to mild clinical findings diagnosed in adulthood (4). Typical findings are short stature, dysmorphic facial appearance, chronic joint pain, skeletal system involvement, cardiac involvement, hepatosplenomegaly, and carpal tunnel syndrome (CTS) at an early age (4). The incidence of CTS has increased in MPS, especially in types I, II, IV A, and VI, due to GAG accumulation in tissues (5,6). Since the frequency of CTS increases in these subgroups, screening is recommended (7-9). However, focusing on diagnosis, examination, and treatment regarding the involvement of patients' more vital organs, such as the cardiac, respiratory, and central nervous systems, may delay CTS screening (7-9). In addition, findings such as mental retardation and claw hands in patients may overshadow CTS symptoms and delay the diagnosis of CTS in MPS patients (7-9). In the literature, CTS screening is recommended annually in MPS patients (10,11). Still, electromyography (EMG) examinations cannot be performed or are delayed due to the patient's mental retardation, young age, agitated behavior, inability to cooperate with EMG examination, and sometimes require additional procedures such as sedation (10,11). We planned this study because we hypothesized that detecting the presence of CTS with another system involvement may be beneficial in excluding inappropriate patients from CTS screening and directing appropriate patients to EMG examination for CTS screening without delay. Cardiac involvement in MPS is among the system involvements that can be detected in the early stages with decreased exercise capacity and hearing cardiac murmur on physical examination (12). Common cardiac findings include heart valve thickening, valve dysfunction (especially in the mitral and atrial valves), and cardiac hypertrophy (12). Conduction system, coronary artery, and vascular involvement may be less commonly observed (12). Cardiac findings are necessarily reviewed by clinicians in the clinic during follow-up examinations, as they are insidiously progressive and responsible for early mortality (12).

In the MPS, GAG accumulation is responsible for the disease, which occurs at different levels in various tissues (1). This difference has caused clinical findings to vary in each patient and subgroup. However, whether there is a relationship between system involvements has not been investigated before in the literature.

In this study, we aimed to investigate the relationship between cardiac involvement findings detected by echocardiographic imaging and CTS in MPS patients who underwent EMG for CTS screening.

Materials and Methods

The study was conducted as a cross-sectional study between May 12, 2023, and June 30, 2024. In this cross-sectional study, EMG results of patients' CTS screening were obtained from file data, and echocardiographic examinations were performed within the specified dates. Ethics committee approval was obtained before starting the study (Selçuk University local ethics committee, Decision No: 2023/302, date: 06/06/2023). The necessary informed consent for the study was obtained from the patients and/or their legal guardians, and the study was conducted following the Declaration of Helsinki.

This study included patients who were followed up at Selçuk University Faculty of Medicine, Department of Pediatric Nutrition and Metabolism, and who were diagnosed with MPS Types I, II, IV A, and VI enzymatically and genetically, and who underwent EMG to screen for CTS and transthoracic echocardiography (TTE) for cardiac involvement. Patients between the ages of 2 and 20 were included. Patients whose diagnosis of MPS was not genetically confirmed, those with other concomitant diseases that could cause CTS (diabetes, gout, pregnancy, rheumatoid arthritis, renal failure, thyroid disease, and lymphedema, etc.), and patients who did not have EMG and TTE examinations were excluded from the study. The EMG examinations of the patients were evaluated based on the EMG reports interpreted by the neurologist and recorded in the patient file information. The electrodiagnosis of CTS in our patients was based on the age-matched reference values of nerve conduction published by Ryan et al. (13). TTE examinations of the patients were performed by pediatric cardiologists blinded to CTS information. In TTE examination, patients without heart valve involvement were categorized as "none", and those with heart valve involvement were categorized as "mitral valve involvement", "aortic valve involvement", "combined involvement of mitral and aortic valves", and "tricuspid valve involvement" according to the heart valve involved. The severity of heart valve involvement is "none" in patients with normal TTE or patients with heart valve involvement but does not cause valve insufficiency/stenosis, "mild" in patients with mild or first-degree heart valve insufficiency/stenosis level, "moderate" in patients with second-degree heart valve insufficiency/stenosis. 3rd-4th degree heart valve insufficiency/stenosis was evaluated as "severe". Left ventricular hypertrophy

was classified as "cardiac hypertrophy," and loss of ventricular function due to ventricular enlargement was classified as "ventricular dilatation." Atrial septal defect (ASD), ventricular septal defect (VSD), patent foramen ovale (PFO), bicuspid aorta, and arcade mitral valve anomalies were accepted as congenital heart diseases. The presence of any of the above-mentioned TTE findings was classified as "cardiac involvement," and the absence of them were classified as "no cardiac involvement."

The data collection form recorded the patients' sociodemographic characteristics (age, gender), MPS subtypes, genetic results, age at diagnosis, ERT status and duration of ERT if any, time between EMG and TTE examination date, EMG findings (classified as present or absent in terms of the presence of CTS findings), and TTE findings.

Statistical analysis

Statistical analyses were performed using SPSS 26.0 for Windows. Descriptive criteria: They are presented as mean and standard deviation, median and minimum-maximum values, percentage, and distribution. The suitability of the data for normal distribution was checked with the Shapiro-Wilk test. Mann-Whitney U test was used to compare continuous variables, and chi-square analysis was used to compare distributions. The significance level was taken as $p < 0.05$.

Results

The sociodemographic characteristics of the patients, the distribution of MPS subtypes, and data on diagnosis and treatment processes were summarized in Table 1. Twenty-six MPS patients who met the criteria were included in the study. The mean age (mean±SD) of the patients was 128±58 months. Ten (38.5%) of the patients were female. The most common MPS subtype was MPS Type IV A with 12 (46.2%) patients. The average time between EMG and TTE examinations was 8±5.5 months. Twenty-two (84.6%) of the patients were receiving ERT. The mean (mean±SD) duration of receiving ERT was 44.3±51.6 months.

Table 1. Evaluation of patients' sociodemographic characteristics, diagnosis, and treatment processes

		n	%
Gender	Female	10	38.5
	Male	16	61.5
MPS subtype	I	6	23.1
	II	3	11.5
	IV A	12	46.2
	VI	5	19.2

	Mean	SD
Age (month)	128	58
Age at diagnosis (month)	73.4	57.2
Duration of ERT (month)*	44.3	51.6
Time between EMG and TTE examinations (month)	8	5.5

n: number, %: percent, mean: average, SD: Standard deviation, MPS: mucopolysaccharidosis, ERT: enzyme replacement therapy, EMG: electromyography, TTE: transthoracic echocardiography, *The duration of patients receiving ERT was calculated according to the EMG recording date.

TTE findings of the patients according to MPS subtypes were evaluated in Table 2. There was cardiac involvement in 21 (80.8%) of the patients. Heart valve involvement was present in 20 (76.9%) patients. All five patients without cardiac and six without heart valve involvement were in the MPS type IV A subgroup. Among those with valve involvement, the least affected tricuspid valve was present only in the MPS Type IV A subgroup and was present in one patient. When the severity of heart valve involvement was evaluated, mild valve involvement was the most common in 11 patients, severe valve involvement was present in one patient, and this patient was in the MPS Type VI subgroup. Ventricular dilatation was detected in one patient each from the MPS Type I and MPS Type VI subgroups, while two patients with cardiac hypertrophy were in the MPS Type VI group. Congenital heart disease was present in 6 patients. None of the MPS type I patients had congenital heart disease.

The relationship between the presence of CTS and the study data is examined in Table 3. CTS was present in 14 (53.8%) of the patients. While CTS was present in all MPS type I, II, and VI patients, it was not in any MPS type IV A patients. As a result of the statistical analysis, the status of being MPS Type IV A was statistically significantly higher in the group without CTS than in the group with CTS ($p<0.001$). The presence of cardiac involvement, combined involvement of the aortic and mitral valves, and the severity of heart valve involvement were found to be statistically significantly higher in the patient group with CTS than in the patient group without CTS ($p=0.007$, $p=0.005$, $p=0.009$, respectively).

Discussion

The literature has reported that cardiac involvement

Table 2. Evaluation of transthoracic echocardiographic findings according to MPS subtypes

		MPS Type I	MPS Type II	MPS Type IV A	MPS Type VI
		n (%)	n (%)	n (%)	n (%)
Cardiac involvement	No	0 (0)	0 (0)	5 (41.7)	0 (0)
	Yes	6 (100)	3 (100)	7 (58.3)	5 (100)
Heart valve involvement	No	0 (0)	0 (0)	6 (50)	0 (0)
	Mitral valve involvement	3 (50)	1 (33.3)	4 (33.3)	1 (20)
	Aortic valve involvement	0 (0)	1 (33.3)	1 (8.3)	0 (0)
	Combined involvement of mitral and aortic valves	3 (50)	1 (33.3)	0 (0)	4 (80)
	Tricuspid valve involvement	0 (0)	0 (0)	1 (8.3)	0(0)
Severity of heart valve involvement	No	0 (0)	0 (0)	7 (58.3)	0 (0)
	Mild	4 (66.7)	1 (33.3)	3 (25)	3 (60)
	Moderate	2 (33.3)	2 (66.7)	2 (16.7)	1 (20)
	Severe	0 (0)	0 (0)	0 (0)	1 (20)
Cardiac hypertrophy/ventricular dilatation	No	5 (83.3)	3 (100)	12 (100)	2 (40)
	Hypertrophy	0 (0)	0 (0)	0 (0)	2 (40)
	Dilatation	1 (16.7)	0 (0)	0 (0)	1 (20)
Congenital heart disease	No	6 (100)	2 (66.7)	9 (75)	3 (60)
	Yes	0 (0)	1 (33.3)	3 (25)	2 (40)

Table 3. Examining the relationship between the presence of carpal tunnel syndrome and study data

		Patient group without CTS	Patient group with CTS	
		Median (min-max)	Median (min-max)	p value
Age (month)		132.9 (33.8 – 195.1)	125.2 (58 – 230.7)	0.86*
Age at diagnosis (month)		36.8 (9.2 – 184.6)	69.3 (6.1 – 217.2)	0.37*
Duration of ERT (month)		34 (0 – 129)	14 (0 – 161)	0.67*
		n (%)	n (%)	
Gender	Female	5 (41.7)	5 (35.7)	0.76**
	Male	7 (58.3)	9 (64.3)	
MPS subtype	I	0 (0)	6 (42.9)	<0.001**
	II	0 (0)	3 (21.4)	
	IV A	12 (100)	0 (0)	
	VI	0 (0)	5 (35.7)	
Cardiac involvement	No	5 (41.7)	0 (0)	0.007**
	Yes	7 (58.3)	14 (100)	
Heart valve involvement	No	6 (50)	0 (0)	0.005**
	Mitral valve involvement	4 (33.3)	5 (35.7)	
	Aortic valve involvement	1 (8.3)	1 (7.1)	
	Combined involvement of mitral and aortic valves	0 (0)	8 (57.1)	
	Tricuspid valve involvement	1 (8.3)	0 (0)	
Severity of heart valve involvement	No	7 (58.3)	0 (0)	0.009**
	Mild	3 (25)	8 (57.1)	
	Moderate	2 (16.7)	5 (35.7)	
	Severe	0 (0)	1 (7.1)	
Cardiac hypertrophy/ ventricular dilatation	No	12 (100)	10 (71.4)	0.13**
	Hypertrophy	0 (0)	2 (14.3)	
	Dilatation	0 (0)	2 (14.3)	
Congenital heart disease	No	9 (75)	11 (78.6)	0.83**
	Yes	3 (25)	3 (21.4)	

CTS: carpal tunnel syndrome, ERT: enzyme replacement therapy, MPS: mucopolysaccharidosis, *Mann-Whitney U test, ** Chi-square test

is seen in all MPS subtypes and is common and severe in the early stages, especially in MPS Type I, II, and VI patients (12,14). Cardiac accumulation of GAGs causes cardiac pathologies by affecting heart valve structures, heart muscle, and vascular structures such as coronary arteries (14). Heart valve thickening and dysfunction, cardiac hypertrophy, and ventricular dilatation are common cardiac involvements in MPS (12,14). Arrhythmias, coronary artery, and other vascular involvements have been reported less frequently (12). Progressive heart valve involvement, seen in 60-90% of patients with MPS, is the most prominent and common cardiac pathology (15,16). In our study, similar to the literature, cardiac involvement was present in all MPS Type I, II, and VI patients and 50% of MPS Type IV A patients, and heart valve involvement was the most common cardiac involvement detected in 76.9% of the patients. It has been observed that cases of coronary artery disease and arrhythmia reported in the literature are mainly in the adult age group (17,18). None of our patients had arrhythmia or coronary artery disease. This may be because heart valves are more suitable locations for GAG accumulation than other parts of the heart. Additionally, the need for a more extended period for coronary artery involvement and arrhythmia development may be the reason why we see valve involvement more frequently in our young patient group, where we do not see coronary involvement.

Many studies show that heart valve insufficiency is more common than valve stenosis, mitral valve involvement is more common than aortic valve involvement, and left-sided valve (aortic and mitral) involvement is more common than right-sided valve (tricuspid and pulmonary) involvement (15,19-21). Our study detected more left-sided valve involvement than right-sided valve involvement, and mitral valve involvement was more than aortic valve involvement. While one patient had tricuspid valve involvement, none of our patients had pulmonary valve involvement. The literature reports that GAGs are used in lung development and functions, but their excess is associated with pulmonary fibrosis and lung damage (22). MPS disease, which is a breakdown disorder of GAG, results in this substance accumulating excessively in the lungs. Physiological blood circulation transports it to the left heart, which may cause increased GAG exposure and pathological involvement of the left-sided heart valves. The predilection area mainly consists of the left-sided valves in infective endocarditis and acute rheumatic fever valvular involvement (23-25). The pathophysiology underlying the widespread involvement of the aortic and mitral valves in these two diseases and why GAG accumulation occurs in the same valves in MPS patients may be similar. In histopathological examinations of the valve structures of MPS patients, it has been shown that macrophages with intense GAG accumulation in their cytoplasm accumulate throughout the entire valve structure (26).

CTS is the most common entrapment neuropathy of the upper extremity, which develops due to compression of the median nerve in the area where it passes under the flexor retinaculum (27). Pain and paresthesia are at the forefront in patients (27). Early diagnosis of this condition is essential, considering its deterioration in quality of life and its cost to healthcare services (28). MPS disease is one of the most common causes of CTS detected in childhood (29). For this reason, CTS screening in patients with MPS has been found worth investigating in the literature (1). In a systematic review of 24 articles evaluating the method and frequency of CTS screening in patients with MPS, 462 CTS cases with MPS (417 patients with MPS Type I, 22 patients with MPR type II, four patients with MPS type IV A, five patients with MPS type VI and 14 patients with MPS type undetermined) were detected (1). Additionally, in a study that included 24 patients investigating the presence of CTS in patients with MPS, clinical findings supported the presence of CTS in 26%, electrophysiological findings in 77%, and nerve ultrasound in 92% (30). In another study conducted in Türkiye, where wrist ultrasonography was evaluated as an alternative to electrophysiological methods in diagnosing CTS, 54 wrists of 27 MPS patients were scanned, and 30 wrists were found to have CTS (29). Our study found that 14 (53.8%) of our MPS patients had CTS. The presence of CTS in all of our MPS type I, II, and VI patients supported the literature. However, unlike the literature, we could not detect CTS in any of our MPS VI A patients. The literature has reported that the average age of patients diagnosed with CTS is 5.3-9.5 years (MPS type I and II: 5.3 years, MPS type VI: 7.4 years, MPS Type IV A: 9.5 years) (1). The absence of CTS in our MPS type IV A patients in our study may be due to the later onset of CTS in MPS type IV A patients.

Our study is the first to evaluate the relationship between system involvement in MPS disease. It found that cardiac involvement was more common in MPS patients with CTS, as was the combined aortic and mitral valve involvement, and the severity of valve

involvement increased. These findings showed a close relationship between cardiac involvement and CTS in MPS patients. We think CTS screening will be useful in patients with MPS whose cardiac pathology is detected in early cardiac evaluation.

There were some limitations in our study. Since MPSs are classified as rare diseases, it was a limitation that our study group and MPS subtypes consisted of a limited number of patients. Another limitation of our study was that the time between EMG and TTE recordings was not simultaneous. Apart from TTE and electrocardiography evaluation for arrhythmia, other tests, such as 24-hour Holter to evaluate heart rate and rhythm, were not performed on the patients.

Conclusion

Our study determined that all of our patients with MPS Types I, II, and VI, and 53.8% of our study group, had CTS. Our study found that CTS is more common in patients with cardiac involvement, especially in patients where the aortic and mitral valves are affected together. As a result, it seems considerable to screen these patients for CTS. There is a need for a multicenter study involving a larger number of patients on this subject.

Conflict of Interest

The authors declare that there is no conflict of interest.

Financial Disclosure

The authors do not declare any financial support.

Author Contributions

Conceptualization, Data curation, and Formal Analysis: B.K.Y.; Investigation: B.K.Y., M.T.D., A.S., O.B., H.Y.; Methodology: B.K.Y., M.T.D., A.S., O.B., H.Y.; Supervision: B.K.Y.; Validation: B.K.Y.; Writing-original draft: B.K.Y.,M.T.D., A.S., O.B., H.Y.; Writing-review and editing: B.K.Y.,M.T.D., A.S., O.B., H.Y.; All authors have read and agreed to the published version of the manuscript.

Ethical Approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Selçuk University Faculty of Medicine Local Ethics Committee (Decision No: 2023/302, Date: 06/06/2023).

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