

ORIGINAL ARTICLE

## Cardiovascular findings and effects of enzyme replacement therapy in patients with mucopolysaccharidosis type VI

### Mukopolisakkaridoz tip VI'lı çocuklarda kardiyovasküler bulgular ve enzim replasman tedavisinin etkisi

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#### ABSTRACT

**Objective:** The mucopolysaccharidoses (MPS) are an important group of lysosomal storage diseases. Commonly reported cardiac involvement includes mitral leaflet thickening and accompanying prolapsus, regurgitation, and rarely, stenosis. The aim of this study was to evaluate cardiac involvement in patients with MPS type VI.

**Methods:** The study included a total of 13 children with MPS type VI who were admitted to a single pediatric department between 2016 and 2018. Cardiac status was evaluated prospectively with clinical findings, electrocardiography, and echocardiography. The age of the patients (8 boys, 5 girls) ranged between 2 and 14 years (median: 9 years).

**Results:** No arrhythmia was observed in any patient. Thickening of the mitral valve with or without regurgitation and prolapsus was the most common lesion seen. Additional involvement of the aortic valve was detected in 12 (92.3%) patients, and additional involvement of the tricuspid valve in 4 (30.8%). Isolated septal hypertrophy was found in 2 patients, and congestive heart failure in another.

**Conclusion:** Cardiac involvement is frequent in MPS. Mitral valve deformation is the most frequent finding. An echocardiographic examination should be performed periodically even if the patient has no clinical signs of cardiac disease, and any cardiac involvement should be kept under control with medical treatment.

Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome; MPS) is a chronic, progressive lysosomal storage disease characterized with autosomal recessive inheritance and multiple organ involvement. Dermatan sulfate accumulation due to

#### ÖZET

**Amaç:** Mukopolisakkaridozlar (MPS) önemli bir lizozomal depo hastalığı grubu olup, kardiyovasküler sistemde en sık kalp kapakçıkları ve koroner arterlerde tutulum ile kendilerini gösterirler. Bu çalışmada, MPS tip VI tanısıyla izlenen çocuklarda kardiyak tutulumun değerlendirilmesi amaçlanmıştır.

**Yöntemler:** Mukopolisakkaridoz tip VI tanısı ile 2016–2018 yılları arasında izlenen 13 olgunun fizik muayene, elektrokardiyografi ve standart transtorasik ekokardiyografi bulguları geriye dönük olarak değerlendirildi. Hastaların (8 erkek, 5 kız) yaş aralığı 2–17 yaş (medyan 9) idi.

**Bulgular:** Hastaların EKG'lerinde ritim bozukluğu ve iskemi bulgusu saptanmadı. Ekokardiyografide mitral kapakta yetersizliği en sık görülen bulgu idi. Olguların 12'sine (%92.3) aort kapak yetersizliği, dördüne (%30.8) triküspit kapak yetersizliği eşlik ediyordu. İzole septal hipertrofi iki olguda mevcut idi. Bir olguda kapak tutulumuna ek sol ventrikül sistolik fonksiyonlarında bozulma görüldü.

**Sonuç:** Mukopolisakkaridozda kardiyak tutulum herhangi bir zamanda ortaya çıkabilir. Mitral kapak deformasyonu en sık görülen bulgudur. MPS'li olgularda belirgin yakınma ve fizik muayene bulgusu olmasa dahi, ekokardiyografik incelemede kardiyak tutulum saptanmaktadır. Bu nedenle olguların kardiyovasküler değerlendirmeleri düzenli olarak yapılmalıdır.

N-acetylgalactosamine-4-sulfatase (arylsulfatase B) deficiency is seen in patients.<sup>[1-3]</sup>

Mucopolysaccharidosis manifests itself in the cardiovascular system most frequently with involvement of the heart valves and coronary arteries. However,

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myocardial, pericardial and aortic involvement is not uncommon. Often, mitral valve insufficiency is seen secondary to thickening and prolapse of mitral valve. Echocardiographic examinations of patients without significant symptoms and physical examination findings may reveal findings indicating cardiovascular involvement. Generally depending on the level of deficient enzyme, clinical findings may change from mild to heavy form.<sup>[3-5]</sup>

## METHODS

In this study, we present the cardiac findings of 13 children with MPS type VI diagnosed as a result of physical electrocardiographic and echocardiographic examinations. The patients had MPS type VI diagnosis confirmed by DNA analysis and lack of arylsulfatase B activity in fibroblasts. Enzyme replacement therapy (ERT) was initiated in the patients whose enzyme levels and mutation analysis results were compatible with the disease, without multiple sulfatase deficiency and advanced mental deficiency according to Denver Developmental Screening Inventory.

Transthoracic echocardiography was performed by a single cardiologist using the iE33 system echocardiography device (Philips Healthcare, Andover, USA) in accordance with the recommendations of the American Society of Echocardiography.<sup>[6]</sup> Standard two-dimensional, M-mode, color Doppler, PW-Doppler and CW-Doppler images were obtained from parasternal short, long axis and apical four-chamber windows. All measurements were repeated at least three to four times and averaged. Left ventricular end-diastolic diameter (LVEDD), interventricular septum thickness in systole and diastole (IVSs-IVSd), and posterior wall thickness (PWTs-PWTd) were measured in all participants from the standard transthoracic window. Left ventricular ejection fraction (LV EF) was calculated using the Simpson's method.<sup>[7]</sup> The values obtained were compared with the Z-score values calculated according to body surface area.<sup>[8]</sup> Mitral, aortic and tricuspid valve regurgitation were evaluated by using color Doppler from the apical four-cavity and long axis view. Peak valve insufficiency flow rates were obtained by using CW-Doppler technique. The degree of mitral and aortic valve insufficiency was evaluated as mild, moderate and severe according to measurement of vena contracta width.

Informed consent forms were obtained from the families of all participants before the study. Local ethics com-

mittee approval was received for the study protocol (Ethics Committee No: 2018/042).

## Statistical analysis

Study data were evaluated using SPSS (Statistical Package for Social Sciences) for Windows 17.0. Descriptive parameters of the obtained data were given as mean±standard deviation (mean±SD), median, minimum-maximum (min-max) values and percentages (%). In statistical analysis, chi-square test was used for intergroup comparisons of categorical data, and for quantitative variables independent sample t-test and Mann-Whitney U-test were used. Spearman's method was used for correlation analysis. A p value of <0.05 was considered statistically significant.

## RESULTS

Eight male (61.5%) and five (38.5%) female patients with a median age of 9 (range: 2–17 years) years were diagnosed with mucopolysaccharidosis type VI. The clinical presentation of the cases was rapid progressive form in two, moderately and mildly severe clinical form in 4, and 7 cases respectively (Table 1, Fig. 1). At physical examination grade1/6 systolic murmur was heard at the mitral focus in only seven cases. Seven patients (58.3%) were receiving recombinant human arylsulfatase B) (galsulfase, Naglazyme®, Biomarin Corporation) while six (46.2%) cases were not. The characteristics of the study group are presented in Table 1.

## ECG and echographic findings

ECG of the patients did not reveal any rhythm disorder, low voltage or ischemia suggestive of coronary artery disease.

Echocardiographic examination showed mild or moderate mitral valve insufficiency in all cases with or without ERT treatment (Fig. 2). Mitral valve insufficiency was accompanied by mild or moderate aortic valve insufficiency in 12 (92.3%), and mitral valve

### Abbreviations:

ERT	Enzyme replacement therapy
IVSd	Interventricular septum thickness in diastole
IVSs	Interventricular septum thickness in systole
IVSd	Interventricular septum thickness in diastole
LV EF	Left ventricular ejection fraction
LVEDD	Left ventricular end-diastolic diameter
MPS	Mucopolysaccharidosis
PWTs	Posterior wall thickness in systole
PWTd	Posterior wall thickness in diastole

**Table 1.** Demographic characteristics and cardiac examination findings of the cases followed up with the diagnosis of mucopolysaccharidosis type IV

	Age (years)	Gender	Weight (kg)	Follow-up period (year)	Clinical form	Duration ERT	Medications	Echocardiographic findings
N.G.	13	Male	25	2	Orta	3 yrs	Enalapril	MR (moderate); MVP, AR (mild)
Ş.A.	2	Femele	7	1	Hızlı	3 month	Enalapril	MR (moderate); MVP, AR (mild)
Z.Ö.	10	Femele	23	3	Yavaş	3 yrs	None	MR (mild), AR (moderate)
E.K.	7	Femele	21	2	Hızlı	2 yrs	Enalapril, Digoxin, Furosemide	MR (mild), MS (mild), AR (mild), TR (mild) Systolic dysfunction
B.K.	9	Femele	20	2	Yavaş	3 yrs	Enalapril	MR (mild), AR (moderate)
H.G.	11	Femele	18.5	2	Yavaş	1 yrs	Enalapril	MR (mild), TR (mild), PDA
B.A.	10	Male	25	7	Orta	7 yrs	None	MR (moderate), AR (mild), TR (mild)
M.A.	8	Male	19	1	Yavaş	None	None	MR (mild), AR (mild)
E.A.	7	Male	52	3	Yavaş	None	None	MR (mild), AR (mild)
A.E.O.	4	Male	12.5	2	Orta	None	Enalapril	MR (moderate), MVP, AR (mild), TR (mild)
S.Ş.	17	Male	48	3	Yavaş	None	Enalapril	MR (mild), AR (moderate)
N.Ö.	9	Male	22	4	Orta	None	Enalapril	MR (moderate), AR (mild), isolated septal hypertrophy
M.A.Z.	9	Male	20	2	Yavaş	None	None	MR (mild), AR (mild), isolated septal hypertrophy

ERT: Enzyme replacement treatment; M: Moderate progressive; R: Rapidly progressive; S: Slowly progressive; MR: Mitral regurgitation; MVP: Mitral valve prolapsus; AR: Aortic regurgitation; MS: Mitral stenosis; TR: Tricuspid regurgitation; PDA: Patent ductus arteriosus.



**Figure 1.** Phenotypical characteristics of a case with mucopolysaccharidosis Type VI.

insufficiency in four (30.8%). Eight patients (66.6%) had moderate mitral valve insufficiency and mild aortic valve insufficiency with myxomatous change and thickening of the mitral and aortic valves (Fig. 2). There were no significant myxomatous changes in the aortic valve in four patients with mild aortic valve insufficiency.

Of the eight patients with moderate mitral valve insufficiency, 3 (23.1%) had mitral valve prolapse. Any significant difference was not detected in the severity of aortic and mitral valve regurgitation in patients having a moderate or mild clinical course ( $r=0.316$ ;  $p>0.05$ ).

Six of 7 patients who received ERT had moderate mitral valve, and the other one mild aortic valve insufficiency. Among 6 patients who did not receive ERT;



**Figure 2.** Findings of myxomatous changes in mitral valve, and mitral valve regurgitation in two-dimensional color echocardiography.

**Table 2. Degrees of valvular insufficiency as detected on echocardiograms of MPS type VI cases who received and did not receive ERT**

Echocardiographic findings	Degree of valvular insufficiency	Patients who received ERT (n)	Patients who did not receive ERT (n)
Aortic valve insufficiency	None	1	–
	Mild	3	5
	Moderate	3	1
Mitral valve insufficiency	None	–	–
	Mild	1	4
	Moderate	6	2

ERT: Enzyme replacement therapy; MPS: Mucopolysaccharidosis.

**Table 3. Conventional echocardiographic findings in patients followed up with the diagnosis of MPS type VI**

	Patients who received ERT	Patients who did not receive ERT	<i>p</i>
	Mean±SD (min-max)	Mean±SD (min-max)	
Left ventricular ejection fraction (%)	66.1±5.6 (54–70)	69.5±4.1 (67–76)	0.531
Left ventricular fractional shortening (%)	34.4±3.7 (27–39)	38.3±3.2 (35–43)	0.614
Left ventricular end-diastolic diameter (mm)	32.4±4.8 (24–37)	34.6±5.2 (27–42)	0.732
Interventricular septum thickness in diastole (mm)	7.2±0.8 (6–8)	9.3±2.8 (6–13)	0.231
Interventricular septum thickness in systole (mm)	9.2±1.5 (7–10)	11.6±3.2 (8–16)	0.295
Posterior wall thickness in diastole (mm)	7.1±0.8 (6–8)	7.5±1.1 (6–9)	0.443
Posterior wall thickness in systole (mm)	9.1±0.8 (8–10)	10.1±1.9 (8–13)	0.361

ERT: Enzyme replacement therapy; MPS: Mucopolysaccharidosis; SD: Standard deviation; Min: Minimum; Max: Maksimum.

four had mild, and two moderate mitral valve insufficiency, while the remaining patient received the diagnosis of moderate aortic valve insufficiency. There was no significant difference between the patients with and without ERT in terms of valvular involvement ( $p>0.05$ , Table 1). Although the patients with moderate aortic regurgitation and mitral regurgitation were comparatively older, there was no significant correlation between the severity of mitral and aortic valve lesions and age ( $r=0.216$ ;  $p>0.05$ ). When the groups receiving ERT were compared in terms of severity of valve deficiencies, there was no significant difference between the groups, although the greater number of patients with moderate valve insufficiency was receiving ERT ( $p>0.05$ , Table 2). Mitral, aortic and tricuspid valve involvement and left ventricular systolic dysfunction were observed in a seven-year-old patient receiving ERT. Left ventricular systolic dysfunction was detected in this case with mild stenosis of the mitral valve and moderate insufficiency of the aortic and mi-

tral valves. Dilated cardiomyopathy, systolic dysfunction, pulmonary hypertension and arrhythmia were detected in other cases. Isolated septal hypertrophy was not detected during the follow-up of cases excepting two patients who did not receive ERT treatment. Eight (66.6%) of the patients with moderate mitral and aortic valve insufficiency received enalapril, and the patient with left ventricular systolic dysfunction was receiving enalapril, digoxin and furosemide. Cardiac treatment was not given to 5 (38.7%) cases (Table 3). Two-year follow-up of six patients who did not receive ERT did not manifest any significant changes in mitral and aortic valve insufficiencies and wall thickness.

## DISCUSSION

Mucopolysaccharidosis type VI arylsulfatase B develops as a result of a mutation in the the lysosomal enzyme (5q13-5q13) -encoding arylsulfatase B (ARS-B) gene consisting of 8 exons and located on

chromosome 5 (5q13-5q13).<sup>[1,3]</sup> As a result of accumulation of dermatan secondary to enzyme insufficiency dysfunction at the cell, tissue and organ levels develops. The clinical picture is classified into three forms: mild (slowly progressive form), moderate and severe (rapidly progressive form).<sup>[8,10-12]</sup> Often rapidly progressive form, and less frequently slowly progressive form are observed in these patients. Mucopolysaccharidosis has a clinically heterogeneous course which varies dependent on the age of the patient at the onset of symptoms, and rate of disease progression.<sup>[12]</sup>

Respiratory failure, cardiac disease, and spinal cord compression requiring surgical intervention may develop.<sup>[11-13]</sup> In our study, generally, the clinical picture of our cases was in mild and moderate form except two cases.

In addition to coarse facial appearance, hydrocephalus, corneal turbidity, dysostosis multiplex and hepatosplenomegaly, and cardiovascular involvement are frequently seen. The age of onset of complaints is between two and three years in the rapidly progressive form of MPS VI. Respiratory failure, heart disease, severe joint involvement and spinal cord compression that may require surgical intervention may develop. Cases are usually lost in their 20-30s due to heart failure. In the slowly progressive form of the disease, patients may present with mild complaints due to lower enzyme levels. Skeletal complications such as short stature, carpal tunnel syndrome, Dupuytren's contracture and hip dysplasia may develop. Heart valve diseases, obstructive sleep apnea and pulmonary complications may develop in adulthood.<sup>[11-13]</sup> In our study, generally our patients presented with mild and moderate clinical forms of the disease except two cases.

Current articles on cardiovascular involvement in mucopolysaccharidosis predominantly present both adult and pediatric cases, but only a small number of articles have addressed children. It has been reported that different types of cardiac involvement may occur for different types of MPS and the severity of cardiac involvement may be at varying degrees of severity depending on the type of MPS.<sup>[4,5]</sup>

An association has been reported between cardiovascular involvement and accumulation of dermatan sulfate. It has been thought that cardiac lesions are more severe in patients in whom enzymatic defect causes dermatan sulfate deposition (types I, II, VI and VII). Because this glycosaminoglycan is predominantly found in the structure of the valves and vascular bed.<sup>[1-4]</sup>

Although cardiac findings frequently seen in patients are valve diseases, cardiomyopathy may also develop. Left-sided valve lesions, ventricular hypertrophy, and pulmonary hypertension are the most common findings. Clinical findings ranging from asymptomatic valve involvement to extremely severe heart failure may be seen.<sup>[2-4,13]</sup>

The most frequently seen cardiac finding in patients with mucopolysaccharidosis is involvement progressing with deformation of mitral and aortic valves.<sup>[3,4,6,10,11]</sup> Generally in patients with MPS thickening and deformity of heart valves occur as a result of accumulation of myxomatous substance in heart valves.

In the studies performed, mitral valve insufficiency was the most common echocardiographic examination followed by aortic valve and then mitral valve insufficiencies.<sup>[4,5]</sup> The most common cardiac finding in our study was mitral valve thickening and myxomatous change and mitral valve insufficiency followed by aortic valve insufficiency. It has been reported that heart valve disorder was clinically silent at its early stage, but then but with time the disorder might result in valve insufficiency and even stenosis.<sup>[5,14]</sup> In one of our patients, moderate mitral valve insufficiency together with mild degree of mitral valve stenosis developed during follow-up. It has been reported that mitral valve involvement is mostly seen in types I, II and III, and aortic valve in type II and IV.<sup>[1,10,11]</sup> Although in general, cardiac involvement is rarely seen in MPS type VI, in all 13 cases we observed, in accordance with studies that asserted the contrary, we detected various degrees of mitral, aortic and tricuspid valve insufficiencies.

Though valvular involvement in patients with mucopolysaccharidosis was known for years, presence of cardiac hypertrophy in this disease has been defined at a much later date. In some studies, it has been reported that in addition to valvular involvement, left ventricular concentric hypertrophy and isolated septal hypertrophy can be seen in patients with MPS type VI, with annual increases of approximately 7-16% in mitral and aortic valve disorders together with left ventricular hypertrophy and valve involvement.<sup>[10,15]</sup> We detected mildly isolated septal hypertrophy in only two of our MPS type VI patients. It was noteworthy that patients with septal hypertrophy did not receive ERT treatment. We did not detect any significant deterioration in cardiac findings during the two-year follow-up of all our patients, including those that received ERT treatment.

Low ejection fraction, advanced age and MPS type I have been indicated as the most important risk factors that increase the risk of death in mucopolysaccharidosis.<sup>[4,10,12]</sup> In our study, left ventricular systolic function deteriorated in only one patient despite ERT.

Due to the accumulation of non-electrically conductive glucosaminoglycans in the myocardium, low voltage tracings and ventricular arrhythmias may be observed on ECG.<sup>[6]</sup> Surface ECG findings were normal in all of our patients. However, we think that 24-hour ambulatory ECG monitoring may increase the likelihood of detecting arrhythmias in these patients.

Factors involved in the development of pulmonary hypertension are commonly seen in patients with mucopolysaccharidosis.

Left heart valve lesions, glycosaminoglycan deposits in the pulmonary vascular bed, thoracic deformities, frequently recurring pneumonias, and obstructive apnea can cause pulmonary hypertension.<sup>[5,6,9,16]</sup> Apneic episodes have been reported during polysomnography in 80% of the patients with pulmonary hypertension. Unlike adults, pulmonary hypertension was the main cause of death in children rather than left ventricular systolic dysfunction.<sup>[6,16]</sup> We detected mitral, aortic, and tricuspid valve involvement together with decrease in left ventricular functions in only one case. In other cases we did not observe any signs of dilated cardiomyopathy, systolic dysfunction, and pulmonary hypertension. This condition may be explained by the fact that our patients were younger, and their clinical findings were not manifest yet without any severe chest deformity.

Bone marrow transplantation and ERT are among the treatment options. It has been reported that enzyme replacement therapy is effective in the protection of pulmonary and cardiac functions and it also increases survival time. However, contradictory literature data are available concerning the effect of ERT on cardiac findings. In some studies, it was observed that early application of ERT prevented the progression of cardiac valve anomalies and decreased interventricular septum and left ventricular hypertrophy.<sup>[2,9,15]</sup> The most current data in some studies have a tendency to indicate that ERT does not lead to any improvement in valvular anomalies. Besides it does not affect the progression of cardiac involvement, but it is effective in maintaining stability of clinical findings.<sup>[11,13-15]</sup>

In our study, although the number of patients with moderate mitral and aortic valve insufficiency was

higher in the ERT group, we did not find any significant relationship between the severity of valve involvement and ERT. In addition, we did not observe any significant deterioration in cardiac findings in the follow-up of all cases including seven patients who received ERT therapy. We thought that this condition may be due to the fact that cardiac involvement in MPS type VI patients was less frequently seen than other types. Besides, the patients were in the pediatric age group and followed up for a shorter period of time. As in our study, the effect of enzyme treatments on valvular involvement is limited. In a study of patients with mucopolysaccharidosis, the most severe heart disease was reported to be in young MPS VI patients, and ERT was reported to affect left ventricular mass and IVSd, with little or no effect on valvular failure.<sup>[17,18]</sup> Therefore, we think that new treatment options are needed.

Involvement of the mitral and aortic valves in mucopolysaccharidosis is reportedly progressive, so surgical intervention is required. It is important to keep these patients under control with medical treatment during the follow-up.<sup>[12,17]</sup> None of our cases had valvular pathologies requiring surgical intervention. In addition, unlike other studies, we did not find a significant relationship between the severity of valvular lesions and age. We think that this finding of ours may be due to the small number of patients in our study.

In accordance with the literature; echocardiographic changes were more widespread than cardiovascular signs and symptoms. Indeed, thoracic deformities may prevent auscultation and restrict exercise that may be mistakenly attributed to joint lesions and respiratory failure. In addition, an ECG taken to detect cardiac pathology may not be able to detect ventricular hypertrophy because the mucopolysaccharide material is not electrically conductive.

### Limitations of the study

In consideration of accumulation of glycosaminoglycans in myocardium that may affect ventricular filling, retrospective design of the study, and lack of data showing diastolic functions, the first limitation of the study was the inability to evaluate the diastolic functions of the patient. Inability to perform 24-hour-ambulatory ECG monitoring was second limitation of the study because mucopolysaccharide material has not the property of electrical conductivity. In addition, the sample size of the patient group was small and the follow-up period was short.

## Conclusion

Cardiac involvement in children with mucopolysaccharidosis can occur at any time and has a progressive character. Even if the cases are asymptomatic, echocardiographic examinations should be performed at regular intervals and the patients who may require surgical intervention should be kept under control with medical treatment. Furthermore, considering a broader treatment perspective for MPS, it is important to know cardiovascular abnormalities in order to determine the efficacy of treatment reliably.

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**Keywords:** Children; echocardiography; enzyme replacement therapy; mucopolysaccharidoses.

**Anahtar sözcükler:** Çocuk, ekokardiyografi; enzim replasman tedavisi; Mukopolisakkaridoz.