A Rare Disease: Mucopolysaccharidosis Type 6 and Cardiac Involvement: Case Report

Nadir Görülen Bir Hastalık: Mukopolisakkaridoz Tip 6 ve Kalp Tutulumu

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Geliş Tarihi/*Received:* 12.07.2015
Kabul Tarihi/*Accepted:* 11.10.2015

This case report was presented as a poster at 14. National Pediatric Cardiology and Cardiovascular Surgery, 15-18 April 2015, Denizli.

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doi: 10.5336/pediatr.2015-47228

ABSTRACT Mucopolysaccharidosis type 6, also known as Maroteaux-Lamy syndrome, is a rare, multisystemic, progressive disease characterized by somatic involvement of varying severity and normal intelligence. N-acetylgalactosamine-4-sulfatase enzyme is lacking and disfunction at cell, tissue, and organ levels occurs due to dermatan sulfate accumulation. Besides the findings such as coarse facial appearance, hydrocephalus, dysostosis multiplex, corneal opacity, hepatosplenomegaly, and joint stiffness, cardiac involvement is also frequently observed. Valvular heart disease, cardiomyopathy, and arrhythmia may occur in patients. In this article, we presented and discussed a mucopolysaccharidosis type 6 patient having moderate mitral valve regurgitation together with dextrocardia as a case in the light of recent literature.

Key Words: Mucopolysaccharidosis VI; child; heart valve diseases

ÖZET Mukopolisakkaridoz tip 6, diğer adıyla Maroteaux-Lamy sendromu, değişen şiddetlerde somatik tutulum ve normal zeka ile karakterize, nadir görülen, multisistemik ve ilerleyici bir hastalıktır. N-asetilgalaktozamin-4-sülfataz enzimi eksiktir. Dermatan sülfat birikimi ile hücre, doku ve organ düzeyinde fonksiyon bozukluğu olur. Kaba yüz görünümü, hidrosefali, disostozis multipleks, korneal bulanıklık, hepatosplenomegali ve eklem sertliği gibi bulguların yanında kalp tutulumu da sık görülür. Hastalarda valvüler kapak hastalıkları, kardiyomiyopati ve aritmiler oluşabilir. Bu olgu sunumunda, orta derecede mitral kapak yetmezliği ile birlikte dekstrokardisi olan mukopolisakkaridoz tip 6 hastası son literatür bilgileri ışığında tartışıldı.

Anahtar Kelimeler: Mukopolisakkaridoz VI; çocuk; kalp kapak hastalıkları

Turkiye Klinikleri J Pediatr 2015;24(4):169-72

Mucopolysaccharidosis (MPS) is an inherited storage disease in which the enzymes that break down glycosaminoglycans (GAG) are lacking. Glycosaminoglycans accumulate intralysosomally and disfunction in cells, blood vessels, and organs begin to occur. There are 11 different types of MPS according to deficient enzyme.[1,2] Mucopolysaccharidosis types have many common characteristics, such as somatic involvement properties and being normal at birth but presenting a chronic and progressive course over time.[3,4] Mucopolysaccharidosis type 6, also known as Maroteaux-Lamy syndrome, is a very rare disease; first defined by Maroteaux et al. in 1965. N-acetylgalactosamine-4-sulfatase enzyme (Aryl-

sulfatase B enzyme) is lacking, causing dermatan sulfate accumulation in tissues. In prevalence studies, incidence of all MPS ranges from 2 to 4 cases per 100,000 live births, while the frequency of MPS type 6 has been found to be 0.23 cases per 100,000 live births.[3,5] Patients present with dysmorphic features, short stature, growth retardation, hepatosplenomegaly, conductive hearing loss, corneal opacity, blindness, dysostosis multiplex, joint contractures, frequent upper respiratory tract infection, hypertrichosis, hydrocephalus, umbilical or inguinal hernias, and spinal compression.[6,7] Unlike other types of MPS, mental retardation or other neurological abnormalities are not expected with this disease. Severity of the disease can be graded as (mild, moderate, and severe) and has been identified according to age of onset and clinical findings.[8]

Mucopolysaccharidosis type 6 is usually diagnosed late or incorrectly, as in our patient, and it is frequently confused with other types of MPS. Therefore, initiation of enzyme replacement therapy (ERT) is delayed.[2,3] Cardiac involvement is also a common and expected condition in mucopolysaccharidosis; the onset and degree of cardiac involvement varies depending on disease type.[2,9] In this article, a patient with a diagnosis of MPS type 6, valvular heart involvement, and mirror image dextrocardia are presented as a case and the disease is discussed in the light of current literature.

CASE REPORT

A female patient investigated due to macrocephaly and coarse facial appearance was diagnosed as MPS type 4 at the age of one and she was taken under follow-up. The diagnosis was changed as MPS type 6 a month ago because of the low level of arylsulfatase enzyme in enzyme analysis performed from peripheral blood, so the initiation of ERT was planned. Family history revealed a consanguineous marriage between her parents and that there was no similar disease in the family. During physical examination, body weight of 14 kg and height 90 cm (both less than third percentile) were recorded. Vital signs were normal, but macrocephaly, hypertelorism, flat nose, short neck, coarse facial features, corneal opacity, kyphoscoliosis, club foot, and umbilical hernia were detected. In cardiologic examination, there was systolic murmur of grade III/VI which was heard best in the left precordium. There were no signs of heart failure. Sinus rhythm was observed at the rate of 130 beats/min in electrocardiogram and the heart was in the dextrocardia position in telecardiogram (Figure 1). Echocardiographic imaging was performed, revealing that the mitral valves were thick and there was moderate valve regurgitation with mirror image dextrocardia. Chamber size and heart functions were normal (Left ventricular end-diastolice diameter 34 mm, z score + 2.3, FS 29%) (Figure 2, 3). Patient was followed in outpatient department.

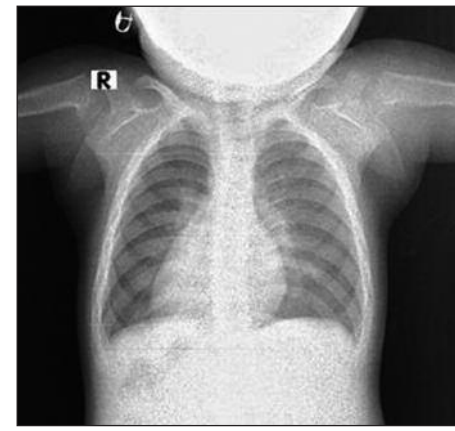

FIGURE 1: Dextrocardia is observed in telecardiogram of patient.

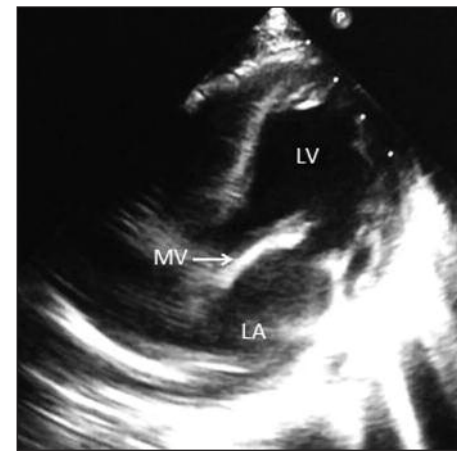

FIGURE 2: Arrow shows thickened mitral valve in echocardiographic examination.

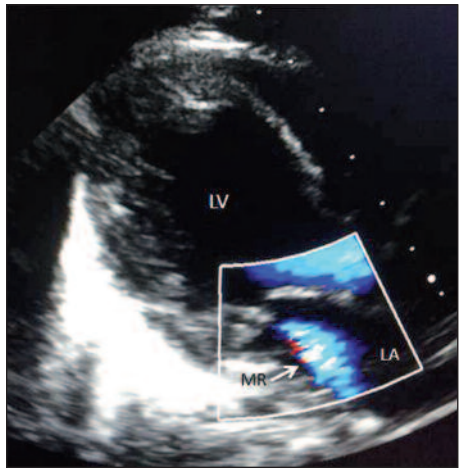

FIGURE 3: Mitral valve regurgitation is observed In echocardiographic examination.

DISCUSSION

Mucopolysaccharidosis type 6 is one of the MPS types in which cardiac involvement is most frequently observed. More frequent and severe cardiac involvement is expected in MPS type 1, 2, 6, and 7, since dermatan sulfate accumulation occurs. Many regions, including myocardial tissue and coronary arteries, may be affected. Primary cardiac involvement is progressive valve degeneration associated with stenosis and/or regurgitation. Regurgitation is most common in mitral valve, secondly in aortic valve. Thickening and stenosis develop in valves due to fibrosis and calcification. Dilated cardiomyopathy, mitral valve prolapse, asymmetric septal hypertrophy, pulmonary hypertension and arrhythmias may occur and patients may apply to doctor with congestive heart failure associated with valvular pathology.[7,10] There may also be symptoms such as shortness of breath, fatigue, palpitations, and rapid breathing, depending on how severe the heart is affected. The most common finding in cardiac examination is murmur with a pathological character usually due to mitral valve regurgitation. In the electrocardiographic examination, long QT interval, ventricular premature beats, supraventricular tachycardia, atrioventricular block, right or left ventricular hypertrophy, and atrial enlargement may be observed. If valve regurgitation is severe, cardiomegaly may occur in telecardiogram and deterioration in cardiac function or arrhythmias may occur due to increase in volume load.[10,11] Our case also displayed the typical symptoms of the disease and cardiac involvement. There has been no association of MPS disease and dextrocardia in the literature. We think our case is the first MPS type 6 patient with dextrocardia in literature.

No treatment method eliminating all symptoms of the disease has been found yet. In addition to supportive treatments, special treatments for the disease, such as ERT, can be implemented by using hematopoietic stem cell transplantation and arylsulfatase enzyme preparation.[9] This may be useful for the prevention of some organ involvement. Enzyme therapy must be used for lifetime via intravenous infusion at a dose of 1 mg/kg weekly and it is expensive. Its positive effects on organ involvement, such as heart valves and bone deformities, are limited. It has some benefits though, such as reduction in organomegaly, reduction in limited joint mobility, increase in physical endurance, and reduction in the amount of GAG in urine. In one study where two sisters were compared in terms of cardiac involvement by echocardiographic investigation. When ERT was initiated with recombinant human arylsulfatase B at early and late periods, progression in cardiac involvement slowed down in the patient that received treatment since the early period. Immediate initiation of treatment with early diagnosis and regular continuation of treatment are crucial to achiev the best results.[11,12] It has been observed in the studies that when ERT is initiated in the late period, there is no pause in the progression of cardiac involvement and cardiac lesions get worse if the treatment is disrupted. There are continuing studies on new treatments such as intrathecal ERT, gene therapy, and anti-inflammatory drugs.[13] ERT had not been started until the age of four in our case, since she had been followed up as MPS type 4.

In patients with mitral or aortic valve regurgitation, they should be followed up with echocardiography to assess the valve regurgitation, heart cavity, and heart functions. In patients with heart failure due to valvular disease, diuretics, an-

giotensin converting enzyme inhibitors, digoxin, and ß blockers can be used. There have been publications about positive effects of furosemide, spironolactone, and carvedilol in literature but the prognosis is generally poor. Surgical treatment may be considered in patients with severe valvular pathology.[7,14] Death is common in the first and second decades due to ventricular arrhythmias, heart failure, or pulmonary infections. There may also be sudden cardiac death.[1,9]

In conclusion, there is a close relationship between cardiac involvement and mortality in patients with MPS. Regular follow up should be conducted for the progression of cardiac involvement; patient should be evaluated by physical examination, electrocardiographic and echocardiographic examinations. If patients with Mucopolysaccharidosis type 6 receive ERT regularly in the early period, milder heart involvement or slower disease progression can be achieved.

REFERENCES

1. Deepak TA, Krishna S, Taretia R. Maroteaux-Lamy syndrome: a rare case of Mucopolysaccharidosis. J Int Oral Health 2010;2(2):1-6.
2. Kuptanon C, Pangkanon S. Review of mucopolysaccharidosis diseases at the Queen Sirikit National Institute of Child Health in the past 15 years. J Med Assoc Thai 2014;97 Suppl 6:S142-6.
3. Kılıc M, Sivri Kalkanoglu SH, Tokatli A, Dursun A, Coskun T. [Mucopolysaccharidosis: Hacettepe experience for 3 years]. J LSD 2010;2(1):83.
4. Baehner F, Schmiedeskamp C, Krummenauer F, Miebach E, Bajbouj M, Whybra C, et al. Cumulatice incidence rates of the mucopolysaccharidoses in Germany. J Inherit Metab Dis 2005;28(6):1011-7.
5. Maroteaux P, Lamy M. Hurler's disease, Morquio's disease and related mucopolysaccharidoses. J Pediatr 1965;67(2):312-23.
6. Kantaputra PN, Kayserili H, Guven Y, Kantaputra W, Balci MC, Tanpaiboon P, et al. Clinical manifestations of 17 patients affected with mucopolysaccharidosis type VI and eight novel ARSB mutations. Am J Med Genet A 2014;164A(6):1443-53.
7. Golda A, Jurecka A, Opoka-Winiarska V, Tylki-Szymańska A. Mucopolysaccharidosis type VI: a cardiologist's guide to diagnosis and treatment. Int J Cardiol 2013;167(1):1-10.
8. Zheng J, Huang Y, Zhao X, Sheng H, Cheng J, Zhou Z, et al. [Analysis of clinical features and arylsulfatase B gene mutation in thirteen Chinese children with mucopolysaccharidosis type VI]. Zhonghua Er Ke Za Zh 2014;52(6): 403-8.
9. Giugliani R, Herber S, Lapagesse L, de Pinto C, Baldo G. Therapy for mucopolysaccharidosis VI: (Maroteaux-Lamy syndrome) present status and prospects. Pediatr Endocrinol Rev 2014;12 Suppl 1:152-8.
10. Golda A, Jurecka A, Tylki-Szymanska A. Cardiovascular manifestations of mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome). Int J Cardiol 2012;158(1):6-11.
11. Kampmann C, Lampe C, Whybra-Trümpler C, Wiethoff CM, Mengel E, Arash L, et al. Mucopolysaccharidosis VI: cardiac involvement and the impact of enzyme replacement therapy. J Inherit Metab Dis 2014;37(2):269-76.
12. Hasanoglu A, Ezgu FS, Tumer L, Kasapkara CS, Okur I, Kucukcongar A. Outcomes of Enzyme Replacement Therapy for Mucopolysaccharidosis Type VI: Gazi University Experience. J LSD 2011;3(1):1-3.
13. Leal GN, de Paula AC, Morhy SS, Andrade JL, Kim CA. Advantages of early replacement therapy for mucopolysaccharidosis type VI: echocardiographic follow-up of siblings. Cardiol Young 2014;24(2):229-35.
14. Jurecka A, Golda A, Opoka-Winiarska V, Piotrowska E, Tylki-Szymańska A. Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome) with a predominantly cardiac phenotype. Mol Genet Metab 2011;104(4):695-9.