Echocardiographic Findings in Some Metabolic Storage Diseases

Filiz ŞENOCAK, M.D., Muhsin SARÇLAR, M.D.,
and Süheyla ÖZKUTLU, M.D.

SUMMARY

This study was planned to determine the presence and extent of cardiac involvement in metabolic storage diseases, including types I and II glycogenoses, Gaucher and Neimann-Pick diseases, galactosialidosis and mucopolysaccharidosis. M-mode, 2-dimensional and Doppler echocardiographic studies were used for the determination of left ventricular wall thickness, systolic function, anatomic derangement, valvular dysfunction and left ventricular diastolic function in the patient and control groups. In 19.35% of the cases valvular involvement, and in 59.26% thickening of the left ventricular wall due to metabolic storage, was found. Left ventricular systolic function was in the normal range. The diastolic mitral flow patterns of the cases showed obstructive type changes.

It can be concluded that in this study, besides previously described cardiovascular changes, some new findings have been detected by means of echocardiography in patients with metabolic storage diseases. (Jpn Heart J **35**: 635–643, 1994)

Key words:
Echocardiography Metabolic storage diseases

A number of inborn errors of metabolism cause accumulation of various substances within tissues and lead to pathologic alterations as well as clinical findings.

There is not yet much knowledge about cardiac involvement in storage diseases. For this reason, we examined the echocardiographic findings in a number of metabolic storage diseases, specifically glycogenoses (types I and II glycogen storage diseases), mucopolysaccharidoses, Neimann-Pick disease, Gaucher disease and galactosialidosis.

MATERIALS AND METHODS

Thirty-one patients whose diagnosis of metabolic disease was established by

From the Department of Pediatric Cardiology, Hacettepe University, Ankara, Turkey.
Address for correspondence: Filiz Şenocak, M.D., Kehribar Sokak 9/46-06700 Çankaya, Ankara, Turkey.
Received for publication January 4, 1994.
Accepted March 14, 1994.

tissue biopsy were studied. Of the cases, 16 were female and 15 male. Their ages varied between 3 months and 17 years (mean age: 6.8 years). Their diagnosis was type I glycogenosis (GSD I) in 12, Gaucher disease in 7, Neimann-Pick disease in 5, galactosialidosis in 2, Hunter syndrome in 2, Pompe disease in 1, Hurler syndrome in 1, and mucopolysaccharidosis atypical variant in 1.

Cardiovascular findings were not used as a criterion in patient selection. Seventy-one healthy children were studied for the control group.

A Toshiba Sonolayer SSH-60A echocardiograph was used for M-mode, two-dimensional (2-D) and Doppler studies. All measurements were done over a minimum of 3 cardiac cycles and their mean values obtained. The images were recorded on videotapes and polaroid films.

In parasternal long-axis projection, left ventricular (LV) end diastolic wall thickness, left ventricular end diastolic and end systolic diameters were obtained by the M-mode technique. Ejection fractions and fractional shortenings were calculated by echocardiography.

The cardiac anatomic structures were investigated by the 2-D technique. Continuous wave Doppler technique was used for the assessment of atrioventricular and semilunar valve dysfunction. In 24 patients, pulsed Doppler echocardiographic indices of LV diastolic function were obtained with the sample site just distal to the mitral annulus in the LV inflow area. The patient group consisted of 8 cases with GSD I, 3 patients with Gaucher disease, 2 cases with Neimann-Pick disease, 2 patients with Hunter syndrome and 1 patient with Hurler syndrome. The transmitral blood flow velocity patterns were obtained during rapid ventricular filling (E) and atrial systolic (A) periods and their ratios (E/A) were calculated. The E/A ratios of 24 patients were compared with the E/A ratios of 71 healthy children and the results were evaluated by Student's t test.

One patient with Gaucher disease was evaluated by left and right heart catheterization and cineangiography.

Results

There were no patients requiring hospitalization except the unique case with Pompe disease. The patient with Pompe disease died during hospitalization and the autopsy confirmed the diagnosis (Figure 1).

In six patients (19.35%) with aortic and/or mitral stenosis and/or insufficiency murmurs, 2-D and continuous wave Doppler echocardiographic studies showed valve leaflet thicknesses (Figures 2 and 3) in addition to stenosis and/or insufficiency findings (Figure 4) considered to be due to their primary disease (Table I). 2-D and M-mode echocardiographic studies of these patients showed dense deposits in the valve leaflets, vascular walls, ventricular endocardium and

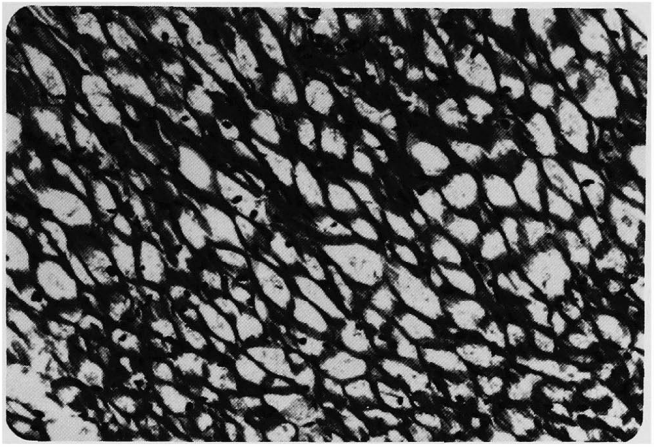

Figure 1. The microscopic appearance of the 28th case with Pompe disease: Cardiomyocytes swollen by the vacuoles containing glycogen are seen (Hematoxylin eosin; ×132).

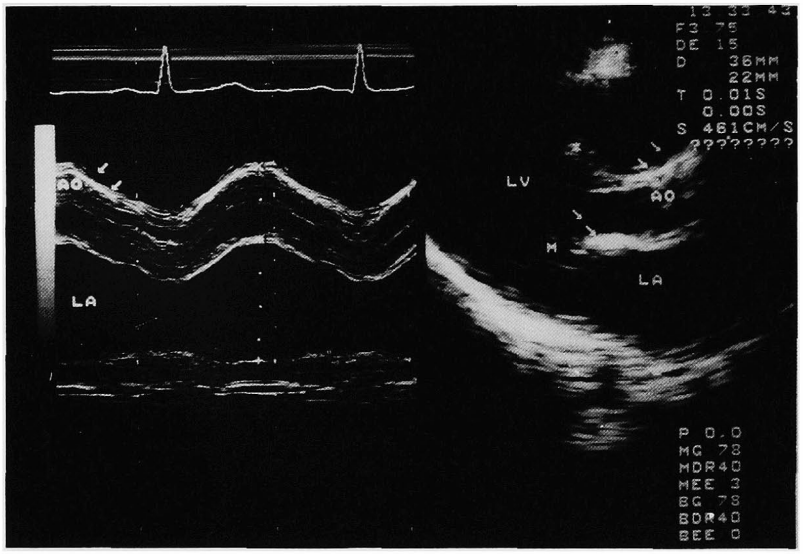

Figure 2. Echocardiographic view of the 11th case in parasternal long axis position. On the right, thickened aortic walls are shown with arrows in 2-D echocardiographic sample. On the left, the same finding is shown with M-mode technique (arrows). AO = aorta; LA = left atrium; LV = left ventricle, M = mitral valve.

myocardium (Figure 5).

The other causes of leaflet damage such as rheumatic fever and rheumatoid arthritis were eliminated by clinical and laboratory methods.

The systolic functions of all patients were in normal ranges.

The end diastolic left ventricular posterior wall (LVPW) and interventricu-

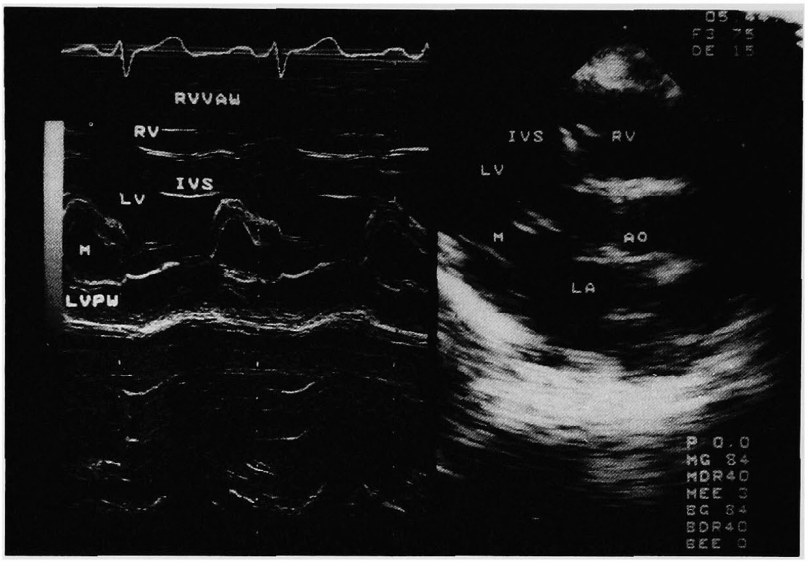

Figure 3. Echocardiographic view of the 29th case in parasternal long axis position. On the left, anterior and posterior mitral leaflet (M) thicknesses are shown with M-mode technique. AO = aorta; IVS = interventricular septum; LA = left atrium; LV = left ventricle; LVPW = left ventricular posterior wall; RV = right ventricle, RVAW=right ventricular anterior wall.

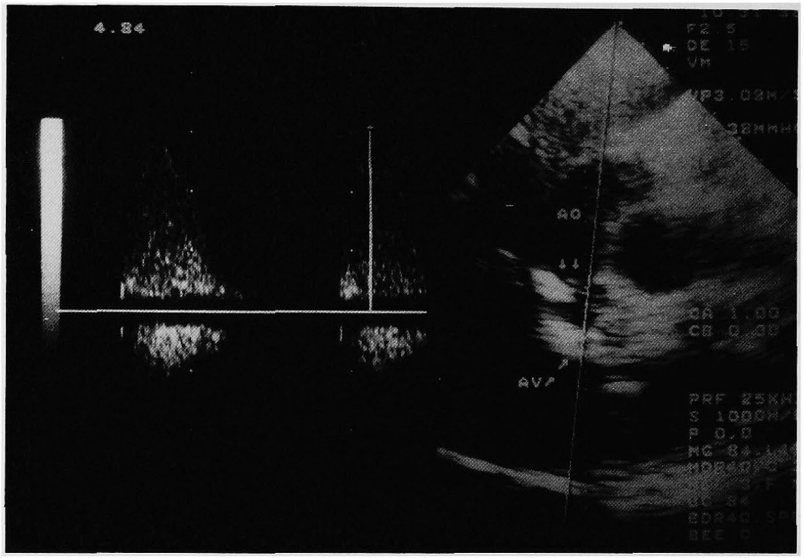

Figure 4. Echocardiographic view of the 11th case in suprasternal view. On the right, aortic wall enlargement is shown with two arrows with 2-D technique. On the left, continuous wave Doppler spectrogram of the 38 mmHg peak systolic gradient at the aortic valvular area is seen. AO = aorta, AV = aortic valve.

Table I. Cases With Valve Involvement

Case No	Age	Sex	Primary disease	Type and degree of involvement		
				Mitral	Aortic	Mitral+aortic
5	6 yrs	F	GSD I		Mild stenosis	
11	12 yrs	F	Gaucher disease			Mild mitral stenosis and insufficiency, mild aortic stenosis
14	3 yrs	M	Mucopolysaccharidosis (atypical variant)	Mild stenosis and insufficiency		
16	8 yrs	M	GSD I	Mild insufficiency		
26	20/12 mos	F	Neimann-Pick disease	Mild insufficiency		
29	11	F	Galactosialidosis			Mild aortic, medium degree mitral insufficiency

*GSD I=Type I glycogenosis

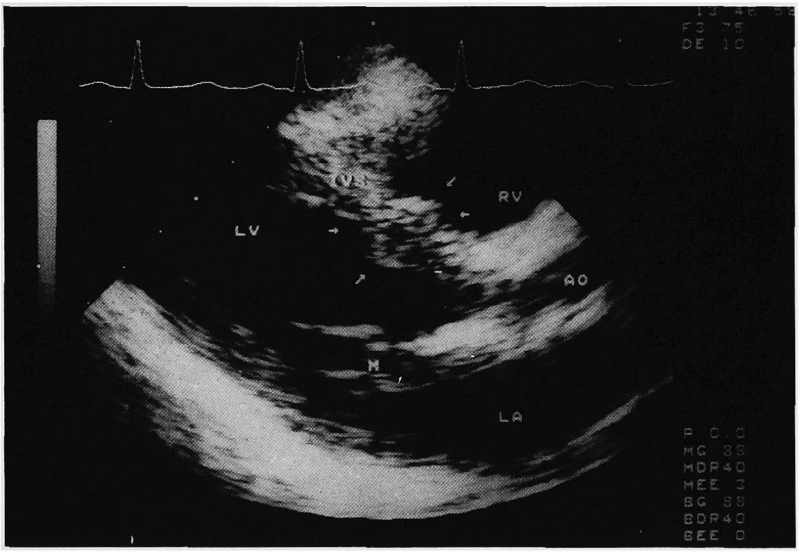

Figure 5. Echocardiographic view of the 11th case in parasternal long axis position. The arrows are showing interventricular septal thickness and echo-dense areas. AO = aorta; IVS = interventricular septum; LA = left atrium; LV = left ventricle; M = mitral valve; RV = right ventricle.

lar septum (IVS) dimensions of 27 patients were compared with normal values for their age (Table II). In 11 patients (40.74%) the LVPW and IVS thicknesses were within normal limits, in 11 cases (40.74%) both the LVPW and IVS, in 3 patients (11.11%) only IVS, in 2 cases (7.41%) only LVPW were found thickened. As a result, 59.26% of patients had left ventricular walls thicker than normal.

Table II. Left Ventricular End Diastolic Wall Thicknesses

Case No	Age (years)	Sex	Primary disease	LVPW (mm)	IVS (mm)	Normal* values
1	7	F	Gaucher disease	7	5	5±1
2	4	M	Neimann-Pick disease	5	5	5±1
3	5	F	GSD I	4	4	5±1
4	14	F	GSD I	6	7	8±1
5	6	F	GSD I	8	8	5±1
6	7	F	Neimann-Pick disease	9	9	5±1
7	6	M	Hunter syndrome	12	15	5±1
8	6	M	Hunter syndrome	11	12	5±1
9	9	M	GSD I	7	7	6±1
11	12	F	Gaucher disease	8	6 (15 in subaortic region)	6±1
12	14	F	GSD I	9	9	8±1
13	17	M	Neimann-Pick disease	8	10	8±1
14	2	M	Mucopolysaccharidosis (atypical variant)	7	6	4±1
15	10	M	GSD I	8	7	6±1
16	8	M	GSD I	7	6	6±1
17	12	M	Gaucher disease	7	8	6±1
18	5	F	GSD I	10	8	5±1
19	1	M	Gaucher disease	6	6	4±1
20	5	M	GSD I	6	6	5±1
21	3	M	GSD I	7	7	4±1
22	3	F	Gaucher disease	5	5	4±1
23	4	F	GSD I	3	3	5±1
24	9	M	Gaucher disease	5	5	6±1
25	7	F	GSD I	6	6	6±1
27	6	M	Neimann-Pick disease	7	7	5±1
28	3/12 months	F	Pompe disease	10	10	4±1
29	11	F	Galactosialidosis	7	10	6±1

GSD I = Type I glycogenosis; IVS = interventricular septum; LVPW = left ventricular posterior wall; *Normal values were obtained from the 17th reference.

Table III. Comparison of the E/A Ratios of 24 Patients with 71 Healthy Children

	Patient group	Control group	p Value
E/A	1.3763±0.3054	1.5596±0.1359	0.004
Range	0.73–2.32	1.34–1.76	$p < 0.05$

The E/A ratios calculated from diastolic mitral flow velocities in 24 patients were compared with the E/A ratios of 71 healthy children and a statistically significant decrease found in the E/A ratios of the patients (Table III).

One of the patients with Gaucher disease underwent cardiac catheterization and 10 mmHg peak systolic pressure gradients between the aortic root and ascending aorta and between the left ventricle and aortic root were found. In

angiography, findings of valvular and supravalvular stenoses were observed.

Discussion

A variety of disorders result from derangements of synthesis, degradation or utilization of certain materials and their subsequent accumulation in a group of tissues including the heart. The cardiac involvement has already been defined in some metabolic storage diseases. For many of them, however the presence or extent of the heart disease has not been entirely recognized.[1-4]

In our series, 19.35% of patients had mild-to moderate degrees of mitral and aortic valvular involvement. In all patients with auscultatory findings of valvular stenosis and/or insufficiency, 2-D and Doppler echocardiographic studies revealed pathologic changes. Cardiac involvement occurs in a high percentage of patients with mucopolysaccharidosis. The most common pathologic findings are thickening of the endocardium, and mitral and aortic valves. In one of our cases with mucopolysaccharidosis, there was mild mitral stenosis and insufficiency. Cardiac involvement in Gaucher disease has been reported in only a few patients, mostly adults with pericardial changes. Recently, mitral and aortic changes were described by Saraçlar et al[5] as in our 11th case. Also, an adult case with dissecting aortic aneurysm was reported by Nasu et al.[6] Sialidosis is a type of glycoproteinoses. Many patients also have a deficiency of β-galactosidase (galactosialidosis).[3] Kelly et al reported a case of sialidosis type II with mitral valve involvement.[7] According to our knowledge, there is no reported case of aortic involvement similar to our 29th case in the English literature. Neimann-Pick disease is one of the lipidoses. In one patient endocardial fibroelastosis was reported.[8] In another patient, cor pulmonale developed secondary to pulmonary infiltration.[9] The mitral pathology of our patient with Neimann-Pick disease is also the first reported mitral involvement in this disorder.

The glycogen storage diseases are inherited abnormalities of glycogen metabolism and comprise over 10 different entities.[10,11] Type I glycogenosis (GSD I) is the most common form of the glycogen storage diseases. In GSD I, the cardiovascular system is usually not affected. However, Pizzo first reported vasoconstrictive type pulmonary hypertension. Following this, a small number of cases with GSD I and pulmonary hypertension have been reported by Furukawa et al and Hamaoka et al.[12-14] Two of our patients with GSD I had mitral and aortic involvement. Our literature survey showed no similar case reported.

M-mode echocardiographic studies showed increased left ventricular wall thickness in 59.26% of cases. This finding is typical for Pompe disease which leads to progressive deposition of glycogen in all tissues of the body, with a predilection for myocardium, skeletal muscle and liver.[1-3,15,16] Also, increased

ventricular wall dimensions have been reported in mucopolysaccharidoses and sialidoses.[3] In Gaucher and Neimann-Pick diseases and GSD I there are no reported cases with thickened ventricular walls in the English literature according to our knowledge.

The intra or intercellular deposition of noncontractile substances disrupts both myocardial contraction and relaxation either by myocyte injury and subsequent fibrosis, or by development of an interstitial intercellular mesoskeleton, which slowly and progressively impairs myocardial compliance. Typically there is preservation of near-normal systolic function.[17] All of our patients, including the one with Pompe disease had normal left ventricular systolic functions compatible with the literature, showing the inadequacy of using left ventricular systolic functions to monitor the progression of the storage diseases. Currently there are no sufficient studies of left ventricular diastolic functions in metabolic storage diseases, but it is proposed that they can be affected by changes in the myocardial fibrils.[17]

The E/A ratios of 24 patients showed a statistically significant decrease compared with those of the healthy children. This finding resembles that of the left ventricular diastolic functions in obstructive cardiomyopathies.[18,19] In 1992 Vinallonga et al. reported a case of type I mucopolysaccharidosis, atypical variant with hypertrophic cardiomyopathy.[20]

In conclusion, our studies showed different types of cardiac involvement in metabolic storage diseases. Some of these findings were already known, and some are new. Without echocardiographic studies, it would be difficult to demonstrate these pathologic derangements. Therefore, it is recommended that children with metabolic storage diseases should be evaluated by echocardiography.

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