Cardiac Involvement in Mucopolipidosis

Importance of Non-Invasive Studies for Detection of Cardiac Abnormalities

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SUMMARY

Although mucopolipidosis, a fatal metabolic storage disorder, is associated with cardiovascular abnormalities, detailed, non-invasive cardiac examinations have not been well documented. We studied 4 children with type II and type III mucopolipidosis, 3 of whom had unequivocal evidence of aortic regurgitation characterized by phonocardiography and M-mode echocardiography. Two-dimensional echocardiography showed an aortic valve prolapse in 3, a mitral valve prolapse in 2 and a tricuspid valve prolapse in 1. The QT interval was prolonged in 2 cases.

In 1 autopsy case, we found considerably thickened and retracted aortic, mitral, and tricuspid valves, and an accumulation of the foam cells in the myocardium. Echocardiography revealed similar findings in another 3 cases.

We conclude that cardiac manifestations in this disorder should be examined carefully particularly by the use of echocardiography which is an excellent technique for detecting cardiovascular abnormalities in mucopolipidosis.

Additional Indexing Words:

Mucopolipidosis   Aortic valve prolapse   Tricuspid valve prolapse   Mitral valve prolapse   QT prolongation in mucopolipidosis

MUCOLIPIDOSIS is an inherited metabolic storage disorder characterized by a Hurler-like appearance, psychomotor retardation and skeletal abnormalities resembling mucopolysaccharidosis. However, excretion of acid mucopolysaccharides is normal.

Since Gilbert et al¹⁾ reported the 4 children with type II mucopolipidosis (I-cell disease) who expired in congestive heart failure, other cardiac mani-

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festations in this disorder have been reported,²⁾⁻⁴⁾ including cardiac murmurs, cardiomegaly, and premature death due to cardiac failure. Despite these reports of clinical abnormalities of the heart, neither phonocardiographic nor echocardiographic studies have been reported previously. This paper presents non-invasive evidence of cardiac involvement in 3 cases and examines the pathological findings in an autopsied case.

CASE REPORTS

The clinical features of the case:

A 14-year-old girl, the first child of unrelated parents and born after uneventful 10 month pregnancy, was first admitted to our hospital at 5 years of age. Psychomotor retardation and a gargoyle-like, coarse appearance were noted, and she had been followed as an atypical Hurler syndrome because of normal urinary excretion of acid mucopolysaccharides. The final diagnosis of type II mucopolipidosis (I-cell disease) was established by observing typical inclusion bodies in cultured skin fibroblasts¹⁾⁻⁴⁾ and the extremely elevated activity of serum lysosomal enzyme.^{5),6)} Her weight was 15 Kg (-5 standard deviation) and her height was 89 cm (-12 standard deviation). Restricted joint mobility and peculiar skeletal changes of the pelvis and spine were present (Fig. 1). Her IQ was 40. On physical examination, her blood

Fig. 1. The general appearance of Case I (N.N.). Note the dwarfism and gargoyle-like features with remarkable joint contractures and umbilical hernia.

Table I. Major Clinical Features of the Patients

Case (Name)	Case I (N.N.)	Case II (T.N.)	Case III (T.O.)	Case IV (S.I.)
Age (years old)	14	9	16	3
Sex	female	male	male	male
Body Weight (Kg)	15 (-5SD)	15 (-3.2SD)	18.5 (-5.6SD)	?
Height (cm)	89 (-12SD)	86 (-8SD)	105 (-11SD)	?
Coarse Face	severe	severe	mild	severe
Mental Retardation	severe (IQ=40)	severe (IQ=43)	mild	severe
Joint Restriction	++	++	+	++
Dysostosis Multiplex	++	++	+	++
Corneal Opacities	+	+	-	+
Hepatosplenomegaly	+	+	-	+
Urinary Excretion of MPS	normal	normal	normal	normal
Inclusion Bodies in Cultured Fibroblasts	+	+	+	+
Classification	ML type II	ML type II	ML type III	ML type II

Abbreviations: IQ=intelligence quotient; MPS=mucopolysaccharides; ML=mucopolipidosis.

Fig. 2. Abnormalities in chest X-ray. The upper print shows the left ventricular enlargement in Case I (N.N.) and the lower print exhibits a deviation of the cardiac silhouette to the right because of the funnel chest in Case II (T.N.). The broad ribs with osteopenia are shown in both cases.

Table II. Cardiovascular Findings

Case (Name)	Case I (N.N.)	Case II (T.N.)	Case III (T.O.)
Chest X-ray	left ventricular enlargement, enlarged pulmonary truncus CTR = 73%	right deviation of cardiac silhouette, aortic dilatation CTR = 63%	left ventricular enlargement CTR = 66%
Electrocardiography	right axis deviation (+135°) ST depression in II, III, and aV _F QT prolongation (0.36 sec) deep S wave in V _{5,6}	LVH ST depression in I, II, III, aV _L , aV _F , V ₃₋₆ increased R wave in V _{1,2}	deep S wave in V _{1,2} ST depression in II, III, aV _F QT prolongation (0.36 sec)
Phonocardiography	aortic ejection sound aortic ejection and regurgitant murmur	aortic ejection sound aortic ejection and regurgitant murmur A ₂ accentuation	aortic ejection and regurgitant murmur A ₂ accentuation
Echocardiography i) M-mode ii) 2DE	fluttering of AML aortic dilatation AVP MVP TVP	fluttering of AML aortic dilatation LVH AVP MVP	fluttering of AML eccentric aortic closure with multiple linear echoes AVP

Abbreviations: CTR = cardio-thoracic ratio; LVH = left ventricular hypertrophy; AML = anterior mitral leaflet; AVP = aortic valve prolapse; MVP = mitral valve prolapse; TVP = tricuspid valve prolapse.

pressure was 98/40 mmHg and heart rate was 120 beats/min. Precordial auscultative findings are described later. There was a mild degree of hepatosplenomegaly and an umbilical hernia. Routine laboratory examinations were normal except for the vacuolation of peripheral lymphocytes.

The patient's profile and clinical features of our 4 cases are listed on Table I. Case I (N. N.; the previously presented patient) and Case II (T. N.) were siblings and diagnosed as type II mucopolipidosis (I-cell disease). Case III (T. O.) was diagnosed as type III mucopolipidosis because of the late onset of symptoms and mild clinical characteristics. Case IV (S. I.) had fatal congestive heart failure and an autopsy was performed to investigate the cardiac abnormalities. Unfortunately, detailed clinical data were not available.

Fig. 3. Electrocardiograms from 3 cases. ST depression is observed uniformly in II, III, and aV_R. Note QT prolongation in Case I (N.N.) and Case III (T.O.)

Non-invasive studies of the heart:

1. Chest X-ray examination (Fig. 2, Table II)

Cardiomegaly and an enlarged pulmonary truncus were observed in all 3 cases. The cardio-thoracic ratio ranged from 63% to 70%. Skeletal abnormalities such as funnel chest and kyphoscoliosis deviated the cardiac silhouette to the right and osteopenia of the ribs was also present.

2. Electrocardiogram (Fig. 3, Table II)

Despite similar clinical findings, the electrocardiograms showed different results in the 3 patients. Case I demonstrated considerable right axis deviation (135°) and a deep S wave in the left precordial leads, while Case II had unequivocal evidence of left ventricular hypertrophy. Case III exhibited a deep S wave in the right precordial leads. None of them showed a conduction disturbance or ventricular arrhythmias. Only Case I had occasional episodes of supraventricular tachycardia, which began at 13 years of age. The most remarkable, uniform finding was ST depression in leads II, III, and aVF, associated with significant QT prolongation with or without ventricular hypertrophy.

3. Phonocardiography

Cases I and II were siblings with type II mucopolipidosis. They had a harsh, systolic ejection murmur, following a loud early systolic ejection sound over the aortic area, and a high frequency diastolic crescendo-decrescendo murmur, with onset at A₂ and its continuation throughout diastole along the

Fig. 4. Phonocardiogram and carotid tracing in Case I (N.N.). The phonocardiogram shows a systolic ejection murmur with a preceding ejection sound (arrow) and a crescendo-decrescendo diastolic murmur, providing a diagnosis of the aortic steno-insufficiency.

Fig. 5. M-mode echograms in Case III (T.O.). The upper figure manifests a fine fluttering of the anterior mitral leaflet (arrow) and the lower presents the eccentric closure of the aortic valve with multiple linear echoes in diastole (arrow).

left sternal border. This is considered to be phonocardiographic evidence of the aortic steno-insufficiency. Neither systolic nor diastolic murmurs were recorded at the apex or the low sternal edge. Phonocardiographic results from Case I are illustrated in Fig. 4. The same findings were obtained, except for the aortic ejection sound (Table II).

4. Echocardiography

a) M-mode study (Fig. 5)

The mitral valve echo exhibited a shaggy fluttering of the anterior leaflet. In addition, the aortic valve was echo-reflective and produced multiple linear echoes throughout diastole, which established echocardiographic characteristics of aortic regurgitation in all 3 children. Moreover, there was an eccentric aortic valve closure, mimicking a congenital bicuspid aortic valve, in Case III. A uniformly hypertrophied left ventricle was detected in Cases I and II.

b) Two-dimensional study (Fig. 6)

Successful two-dimensional images were obtained in all patients either from the parasternal long axis view or from the subcostal four chamber view. The former revealed the aortic cusps and the latter defined mitral and tricuspid valves. In all cases, there was a downward displacement of the aortic

Fig. 6. Two-dimensional echocardiograms. The upper figure shows a long axis view of Case III (T.O.). Note the echo-reflective aortic cusps, which coaptate into the left ventricular outflow tract (an arrow on the right), demonstrating the aortic valve prolapse. The middle figure is the subcostal four chamber view of Case I (N.N.), displaying the high coaptation of the mitral valve into the left atrium, resulting in an unusual systolic "bow" (an arrow on the right drawing, where dotted line is the level of the mitral annulus). This represents the mitral valve prolapse. The bottom exhibits tricuspid coaptation in the right atrium in systole (an arrow on the right, in which the tricuspid annulus is depicted with the dotted line) in the subcostal four chamber view of Case I (N.N.). This indicates tricuspid valve prolapse.

Abbreviations: VS=ventricular septum; LV=left ventricle; LA=left atrium; RV=right ventricle; RA=right atrium.

coaptation toward the left ventricular outflow tract in diastole, resulting in an aortic valve prolapse. One case (Case III) exhibited asymmetric and thickened aortic cusps. The mitral valve was also highly fixed in the left atrium, and it displayed a degree of an unusual systolic "bow" in the adjacent myocardium, showing a severe mitral valve prolapse. The mitral leaflets were also homogeneously thickened. The tricuspid valve in Case II was also thickened and showed systolic displacement of the coaptation of the right atrium. This indicates a tricuspid valve prolapse. The bi-ventricular walls were thickened uniformly, with a diffuse patchy texture like other cardiac storage disorders.

An autopsy study:

Case IV died after developing intractable congestive heart failure, complicated by a severe pulmonary infection. At autopsy, the heart weighed 120 Gm (normal for height age: 54 Gm, normal for chronological age: 72 Gm) and was uniformly hypertrophied. The free margins of the mitral, aortic, and tricuspid valves were thickened and retracted. There were no considerable gross changes on the valvular rings or the chordae tendinae. Microscopic examination of the left ventricle revealed severe vacuolar changes, which included PAS positive granules in myocardial cells.

DISCUSSION

Mucopolipidosis is difficult to diagnose, while the clinical manifestations are characterized as a "Hurler"-like body configuration, coarse facies, marked shortness of stature, multiple skeletal abnormalities, severe mental retardation, occasional corneal opacities and normal urinary excretion of acid mucopolysaccharides.⁴⁾ This disease is thought to be a storage disease which lies between sphingolipidosis and mucopolysaccharidosis.⁷⁾ Diagnostically speaking, it is important to identify the metabolic abnormalities, which are not easy to demonstrate in mucopolipidosis.

Though Gilbert et al¹⁾ stressed the cardiac abnormalities leading to death, few clinical descriptions concerning the heart have been mentioned in the literature.^{2)-4), 8), 9)} In our cases, we found echocardiographic evidence of displacement of prolapsing motion of the mitral valve, the tricuspid valve and the aortic valve.

Two-dimensional echocardiography clearly showed a superior displacement of the coaptation of the mitral valve, resulting in the mitral valve prolapse. M-mode echocardiography did not show posterior systolic bucking or posterior hammocking, possibly because the transducer was placed low on the

deformed chest and was angulated cephalad, which may mask anterior mitral valve motion and produce false negative results. Displacement of the tricuspid valve coaptation was shown echocardiographically and the tricuspid valve prolapse was coexistent with the mitral valve prolapse. The presence of the aortic valve prolapse reflected an increased aortic valve reflection, the eccentricity of the diastolic closure line, aortic root enlargement and fluttering of the anterior mitral valve on M-mode echocardiography. The aortic valve also displayed a downward prolapsing motion toward the left ventricle and an asymmetrical coaptation of the valve during diastole on two-dimensional echocardiography.¹⁰⁾

Since an autopsy case displayed retraction and thickness of the valve edges, these myxomatous, degenerated leaflets probably reflected strong valve echoes and lost collagenous support, resulting in prolapse of the mitral, tricuspid and aortic valves. Aortic root dilatation may also be attributed to the aortic valve prolapse.

It is interesting to note that the mitral valve prolapse accompanied a prolonged QT interval^{11),12)} in mucopolipidosis. This indicates that one should attend to ventricular arrhythmias such as ventricular tachycardias and ventricular fibrillation, because prolongation of the QT interval lengthens the vulnerable period and results in R on T phenomena. Atrial arrhythmias were often experienced in this disease.

Metabolic abnormalities which induce aggregations of foamy cells in the valve cusps and the myocardium result in heart failure which is resistant to digitalis therapy. This condition is sometimes complicated by respiratory infections,^{2)-4),8),9)} and leads to death. In conclusion, it is important to follow the clinical course carefully in order to detect the inevitable impairment of cardiac function, and to treat it as early as possible. Non-invasive techniques such as electrocardiography, phonocardiography, and echocardiography, and two-dimensional echocardiography, are useful to understand what happens in the heart as a result of mucopolipidosis.

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