

Cardiac Manifestations of the Mucopolysaccharidoses

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SUMMARY

The cardiovascular manifestations of the mucopolysaccharidoses (MPS) have not been well characterized. We studied nine children with various forms of MPS, using noninvasive cardiac diagnostic techniques. The echocardiograms of two brothers with Type I H/S MPS showed slow mitral valve early diastolic closure velocities (MVEDC) (18, 29 mm/sec) consistent with mitral stenosis. Each had a soft opening snap, low frequency presystolic murmurs and X-ray evidence of calcific mitral stenosis. Three patients with Type II A MPS had echocardiographic evidence of impaired left ventricular function, suggesting the presence of myocardial damage. One of these had an abnormal electrocardiogram; none had murmurs. No cardiac abnormalities were discovered in two patients with Type III A and IV MPS. One patient with Type VI A MPS had presystolic, holosystolic and early diastolic murmurs. A soft opening snap was recorded. The echocardiogram showed a slow MVEDC (18 mm/sec) and a slightly enlarged left atrial dimension (2.2 cm/m²). In summary, noninvasive studies are useful in evaluating patients with MPS. Type I H/S and Type VI A patients may show evidence of valvular deformity, the former associated with mitral valvular calcification and the latter with both aortic and mitral valve involvement. Type II A patients have muscle function abnormalities and Types III A and IV are shown by noninvasive methods to be free of cardiovascular abnormalities.

THE MUCOPOLYSACCHARIDOSES (MPS) are a group of metabolic disorders characterized by the accumulation of an abnormal intracellular material thought to be an acid mucopolysaccharide. Products of this material are excreted in the urine. Skeletal and soft tissues are affected with a resultant typical facies (fig. 1).

Cardiovascular involvement is known to be present in the mucopolysaccharide syndromes. Coronary artery lesions and mitral and aortic valvular regurgitation have been noted.¹ This report is a systematic study of children with the various MPS syndromes using noninvasive techniques to assess the extent and nature of cardiac lesions present.

Methods

Nine known cases of MPS were studied (tables 1 and 2). No children with Type I H, V or VII were available for study. Two brothers (patients 1 and 2) were classified as MPS I H/S. Skin fibroblasts were cultured and the cells were found deficient in α -L iduronidase both directly by enzyme assay and indirectly by correction with Hurler fac-

tor. These cells were positive for aryl sulfatase B.* The skin fibroblast cells of patient 9 were found deficient in aryl sulfatase B confirming the diagnosis of Type VI MPS.†

All patients had a history, physical examination, phonocardiogram, electrocardiogram, vectorcardiogram (using Frank orthogonal leads), echocardiogram and chest X-ray performed. Phonocardiograms were recorded on an Electronics for Medicine recorder using a band-pass filter to record frequencies of 100-500 cycles per second at a paper speed of 50, 75 or 100 mm/second. Echocardiograms were recorded on a Smith-Kline Ekoline 20 ultrasonoscope with a 2.2 MHz transducer with a one-microsecond transmission time and a repetition rate of 1000 per second using either a Honeywell 1856 strip chart recorder or, for illustrative purposes, an Electronics for Medicine DR12 recorder modified for echocardiographic recordings.

All echocardiographic dimensions were measured from three sequential beats and averaged. The end-systolic dimension (ESD) was measured at the peak of the anterior movement of the left ventricular posterior endocardium. The end-diastolic dimension (EDD) was measured at the R wave of the electrocardiogram. The echocardiographic ejection fraction (EF) was calculated using the formula of Myer et al.² as follows:

$$EF = 1 - .31 \times (ESD/EDD)^2$$

The velocity of circumferential fiber shortening (V_{CF}) was calculated using the following formula:^{3, 4}

$$V_{CF} = \frac{EDD - ESD}{EDD \times LVET}$$

The left ventricular ejection time (LVET) was obtained from the phonocardiographic recording of the carotid pulse

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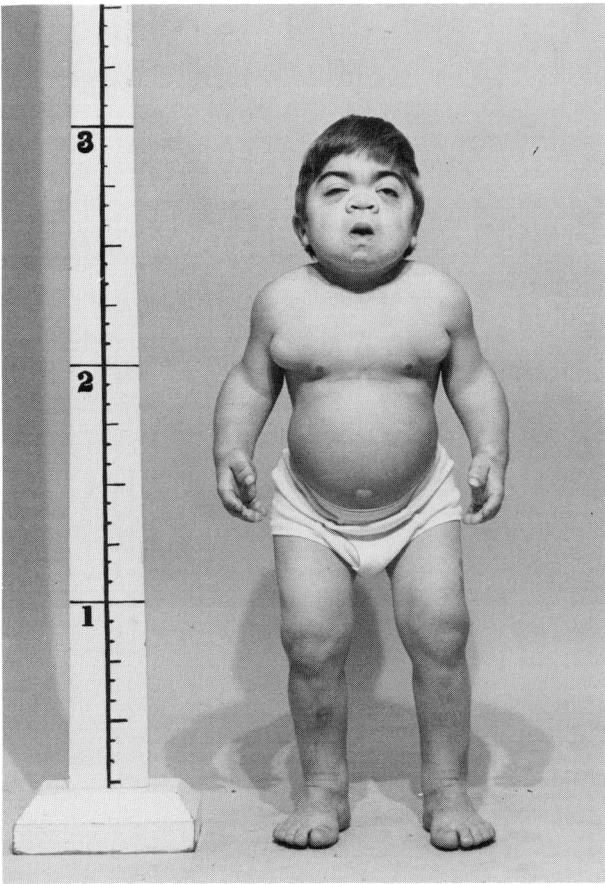


Figure 1

Appearance of patient 9 (Type VI A MPS), age 20. Note the characteristic coarse features and semicrouched stance. The protuberant abdomen is due to hepatosplenomegaly.

and measured during three successive beats which matched the heart rate recorded on the echocardiogram. An average of the measurements was the LVET used in the calculation of the V_{CF} . Left atrial dimension (LAD) was measured by the method of Hirata et al.⁶ Those patients with murmurs of mitral stenosis or regurgitation were also studied by fluoroscopy using an image intensifier.

Results

Two brothers (patients 1 and 2) with MPS Type I H/S were studied. Neither had cardiovascular symptoms. Both had accentuated first heart sounds, opening snaps and rumbling presystolic murmurs. Patient 2 also had systolic and mid-diastolic murmurs (fig. 2). Electrocardiograms of patients 1 and 2 showed prolonged P-R intervals, combined atrial enlargement and increased S waves in the right precordial leads suggestive of left ventricular hypertrophy. These two patients showed slow mitral valve early diastolic closure velocity (MVEDC) of 18 and 28 mm/sec, respectively. Multiple strong echoes were recorded from the anterior mitral valve leaflet and annulus. The posterior mitral valve leaflet echoes were visualized. In patient 2 the posterior leaflet motion was probably abnormal (fig. 3). In patient 1 the posterior mitral leaflet appeared to be moving normally despite the dense, slow moving anterior leaflet echoes. An opening snap was present with a prolonged A_2 -OS interval (0.13 sec); a simultaneous recording of the echocardiogram and phonocardiogram proved that this early diastolic sound was an opening snap and not a ventricular gallop (fig. 4). The left atrial dimension was increased in both. The ejection fraction and V_{CF} were abnormal in patient 2. We were unable to calculate

Table 1

Clinical Data

Patient	Age (yr)	Type MPS	Physical findings	Chest X-ray	Electrocardiogram
1	17	I H/S	Very soft opening snap, diastolic rumble with presystolic accentuation	Calcified mitral annulus	Prolonged P-R interval; combined atrial enlargement; increased posterior forces
2	19	I H/S	Soft opening snap, apical diastolic rumble with soft presystolic accentuation + soft systolic murmur	Calcified mitral annulus	Prolonged P-R interval; combined atrial enlargement; increased posterior forces
3	11	I S	—	—	Normal
4	6	II A	—	—	Ventricular bigeminy
5	2	II A	—	—	Normal
6	8	II A	—	Left atrial enlargement	Normal
7	7	III A	Basal systolic ejection murmur	—	Normal
8	21	IV	Basal systolic ejection murmur	—	Normal
9	20	VI A	Soft opening snap, diastolic rumble with presystolic accentuation, apical blowing holosystolic + aortic early diastolic murmur	Mild cardiac enlargement	Premature ventricular contractions, mild right ventricular enlargement

Table 2

Echocardiographic Data

Patient	Age (yr)	Type MPS	EDD (cm)	ESD (cm)	EF (N = .50)	LVET (sec)	VCF (circ/sec) (N = 1.50)	LAD+ (cm/m ²) (N < 2.0)	MVEDCV (mm/sec) (N > 35)
1	17	I H/S	—	—	—	—	—	4.0	18
2	19	I H/S	4.4	3.2	0.47	0.22	1.24	3.0	28
3	11	I S	3.9	2.7	0.52	0.22	1.40	1.7	70
4	6	II A	4.8	4.0	0.31	0.22	0.76	—	80
5	2	II A	3.5	2.5	0.49	0.28	1.02	2.1	144
6	8	II A	5.0	3.6	0.48	0.22	1.27	1.8	96
7	7	III A	4.5	3.0	0.56	0.22	1.52	1.8	142
8	21	IV	5.3	3.4	0.59	0.23	1.56	1.7	130
9	20	VI A	4.0	2.6	0.58	0.36	0.97	2.2	18

Abbreviations: MVEDC = mitral valve early diastolic closure velocity.

these parameters in patient 1. The chest X-ray revealed calcification of the mitral valve annulus and left atrial enlargement in both (fig. 5).

One patient (case 3) with MPS Type I S had no cardiovascular symptoms or murmurs. The echocardiographic ejection fraction was normal, but the V_{CF} was slightly diminished. The electrocardiogram was also normal.

Three patients with Type II A MPS were studied. None had cardiovascular symptoms. No murmurs were heard. All three had decreased ejection fraction (0.31–0.48) and diminished V_{CF} (0.76–1.27 circ/sec). Occasional episodes of ventricular bigeminy were present in patient 4 with the lowest ejection fraction and V_{CF} of these three patients. Patient 5 had a slightly increased left atrial dimension not supported by X-ray evidence of an enlarged left atrium; while

patient 6 showed mild left atrial enlargement by chest X-ray which was not demonstrated by ultrasound measurement. The vectorcardiograms provided data similar to the electrocardiograms.

One patient each with Type III A and IV MPS were studied. Neither had cardiovascular symptoms. Both patients had basal systolic ejection murmurs. No murmurs of aortic or mitral regurgitation or mitral stenosis were heard. Echocardiographic studies were within normal limits.

One patient with Type VI A MPS was studied (case 9). He had mild exertional dyspnea. His electrocardiogram revealed premature ventricular contractions which disappeared after digitalis was started. The right ventricular voltages recorded on ECG were increased. The chest X-ray showed mild generalized cardiac enlargement. Phonocardiographic recordings demonstrated presystolic, apical holosystolic and early diastolic murmurs consistent with mitral and aortic valve disease. The MVEDC was slow (18 mm/sec) and the left atrial dimension increased. Dense echoes were recorded from the mitral valve annulus. Fragments of the posterior mitral leaflet were seen and the motion appeared abnormal. The EF was normal but the V_{CF} was diminished. Neither chest X-ray nor fluoroscopy revealed calcification of the mitral valve annulus.

Discussion

Seven recognized types of MPS have been described. These are classified both chemically and genetically (table 3). Increased amounts of altered collagenous intracellular substances appear to be deposited in the cardiovascular system within fibroelastic cells.⁷ Damage to the mitral and aortic valves may result. This is probably due both to mucopolysaccharide deposition and collagen derangement. Clinically, this has been manifested by mitral and aortic valvular regurgitation.⁸ Heavy deposits of mucopolysaccharide in the intima of the coronary

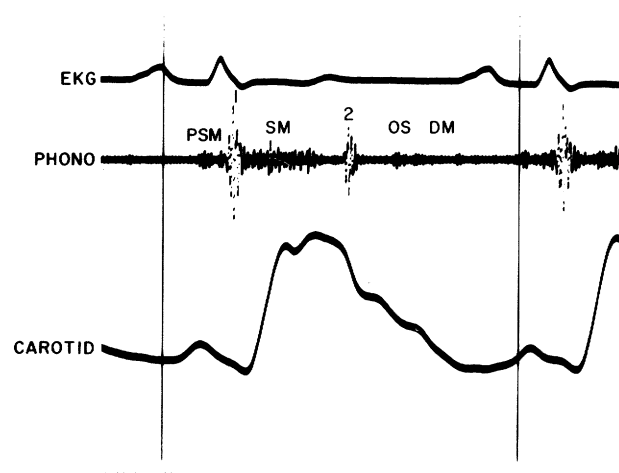


Figure 2

Phonocardiogram recorded from patient 2 (Type I H/S MPS), left sternal border. Characteristic findings of mitral stenosis are seen. Phono = phonocardiogram; PSM = presystolic murmur; 1 = first heart sound; SM = systolic murmur; 2 = second heart sound; OS = opening snap; DM = diastolic murmur. Vertical lines = 1 sec time intervals.

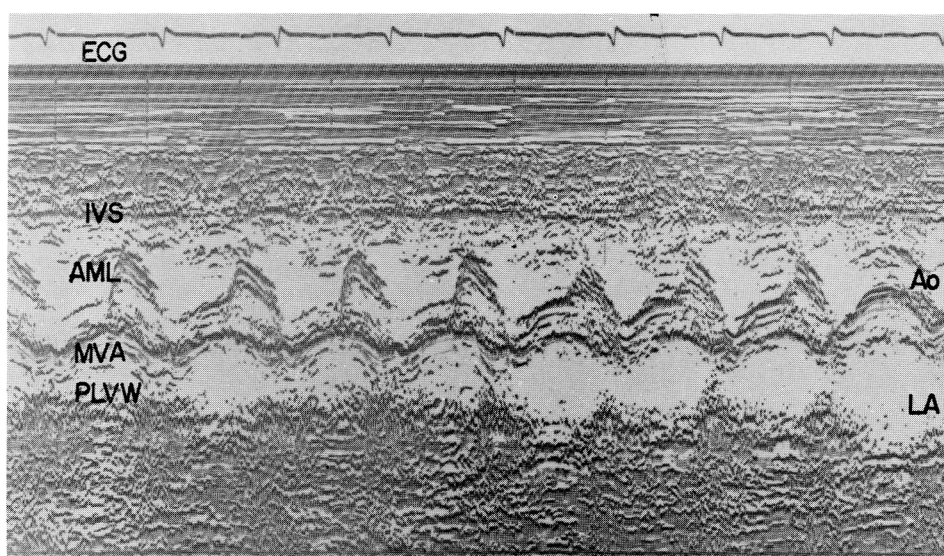


Figure 3

Echocardiogram from patient 2 (Type I H/S MPS). Multiple strong echoes are recorded from the anterior mitral valve leaflet (AML) and the mitral annulus (MVA). The diastolic closure velocity is reduced (28 mm/sec). The posterior mitral valve leaflet is only partially visualized, but appears to be moving abnormally in diastole. IVS = interventricular septum; PLVW = posterior left ventricular wall; LA = left atrium; Ao = aorta.

arteries, aorta and pulmonary artery may produce a pseudo-atherosclerosis.⁹ Previous workers have described patients with Type I MPS dying from car-

diac failure. In these patients no cardiac valvular abnormalities were observed.¹⁰

All previous discussions regarding the cardiac in-

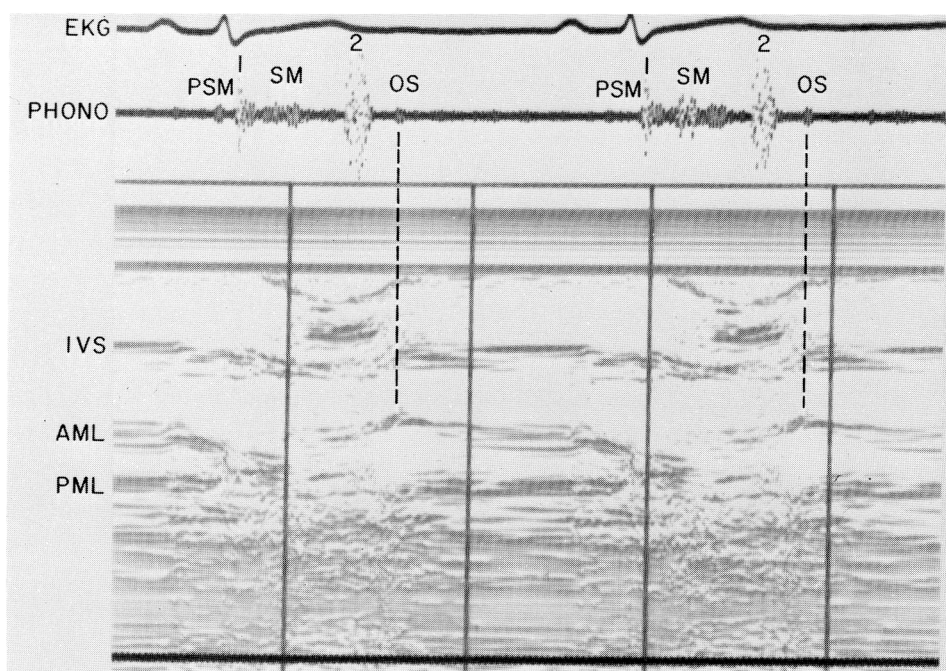


Figure 4

Echocardiogram and phonocardiogram, patient 1 (Type I H/S MPS). Strong echoes are recorded from both mitral leaflets. The diastolic closure velocity is slow (18 mm/sec). The posterior leaflet (PML) appears to be moving normally (i.e., opens posteriorly) in early diastole. An opening snap occurs simultaneously with the maximum separation of the two mitral leaflets (interrupted line). The A₂-OS interval equals 0.13 sec. Vertical lines = 0.5 sec time intervals.

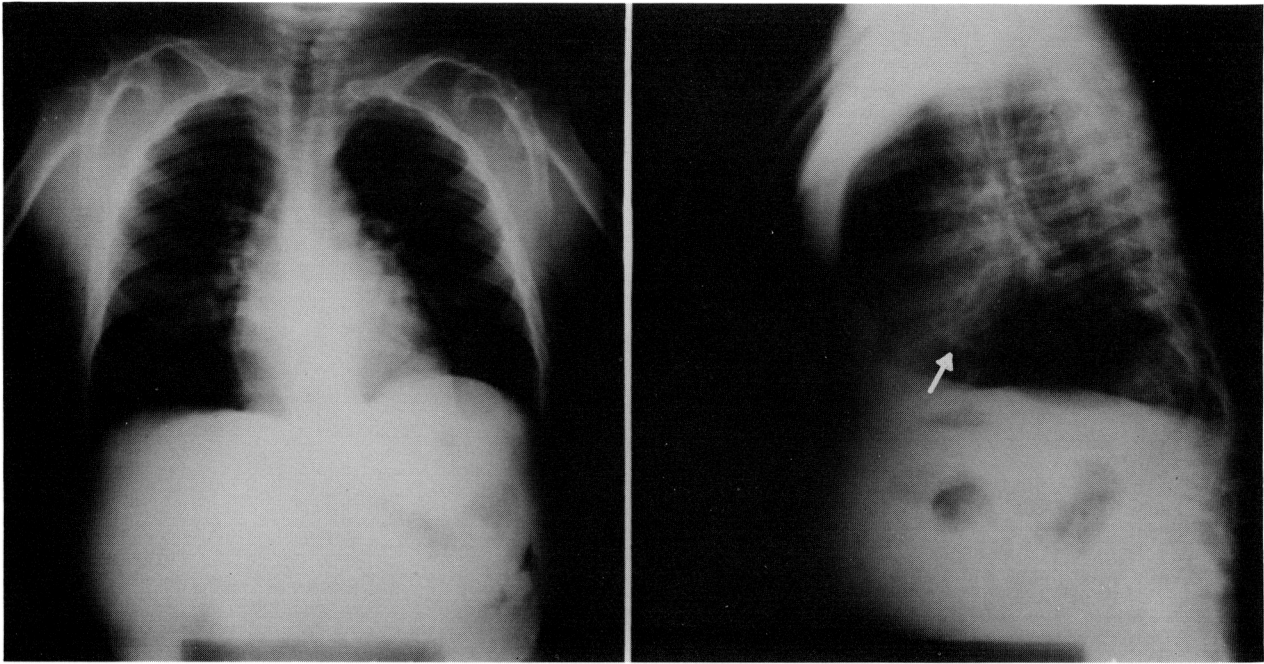


Figure 5

Chest X-ray, patient 2 (Type I H/S MPS). The posteroanterior view (left panel) demonstrates straightening of the left heart border and elevation of the left mainstem bronchus suggesting left atrial enlargement. The lateral view (right panel) shows calcification of the mitral annulus (arrow).

involvement of patients with MPS^{1, 6, 8} have listed a single report of mitral stenosis.¹¹ At autopsy, the mitral valve of this patient was found to be thickened and distorted. The usual abnormalities of collagen fibers were seen. No mention of calcification was made.

Mitral stenosis in our patients is strongly suggested by the presence of typical diastolic and presystolic rumbling apical murmurs documented by phonocardiography and opening snaps shown by simultaneous echo-phonocardiography. In two patients (cases 2 and 9) apical systolic murmurs may represent concomitant

Table 3

Mucopolysaccharidoses

Designation		Excessive urinary MPS	Substance deficient
MPS I H	Hurler syndrome	Dermatan sulfate Heparan sulfate	α -L-iduronidase (formerly called Hurler corrective factor)
MPS I S	Scheie syndrome	Dermatan sulfate Heparan sulfate	α -L-iduronidase
MPS I H/S	Hurler-Scheie compound	Dermatan sulfate Heparan sulfate	α -L-iduronidase
MPS II A	Hunter syndrome, severe	Dermatan sulfate Heparan sulfate	Hunter corrective factor
MPS II B	Hunter syndrome, mild	Dermatan sulfate Heparan sulfate	Hunter corrective factor
MPS III A	Sanfilippo syndrome A	Heparan sulfate	Heparan sulfate sulfatase
MPS III B	Sanfilippo syndrome B	Heparan sulfate	N-acetyl- α -D-glucosaminidase
MPS IV	Morquio syndrome (probably more than one allelic form)	Keratan sulfate	Unknown
MPS V	Vacant		
MPS VI A	Maroteaux-Lamy syndrome, classic form	Dermatan sulfate	Maroteaux-Lamy corrective factor (aryl sulfatase B)
MPS VI B	Maroteaux-Lamy syndrome, mild form	Dermatan sulfate	Maroteaux-Lamy corrective factor (aryl sulfatase B)
MPS VII	β -glucuronidase deficiency (more than one allelic form?)	Dermatan sulfate	β -glucuronidase

Table adapted from McKusick.⁶

mitral regurgitation. The echocardiographic studies showed slow mitral valve closure velocities with multiple strong echoes from the valve and especially the mitral annulus. Multiple strong echoes from the mitral valve and mitral annulus have been described in association with calcific mitral stenosis.¹² There was fluoroscopic evidence of mitral valve annular calcification and left atrial enlargement. The left atrium appeared to be enlarged both by electrocardiogram and echocardiogram.

In all three of the patients with Type II A MPS, one of the two patients with Type I H/S MPS, and the patient with Type VI A MPS, the echocardiographic data of diminished ejection fraction or V_{CF} suggested poor left ventricular performance which in this setting may be the result of coronary artery occlusive disease and/or myocardial disease secondary to mucopolysaccharide deposition. Invasive studies were considered unwarranted in view of the lack of cardiovascular symptoms in these patients.

Noninvasive studies are useful in the assessment of the cardiovascular status of patients with mucopolysaccharidoses. In particular, the patients described herein with Type II MPS appear to have left ventricular dysfunction, while the Type I H/S and VI A MPS patients have mitral stenosis. Calcific mitral stenosis, when detected, may indicate Type I H/S MPS.

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