Cardiovascular studies in the mucopolysaccharidoses

John Nelson, Michael D Shields, H Connor Mulholland

Abstract

Cardiovascular studies were performed on 22 patients with mucopolysaccharidosis ascertained from an epidemiological study on the mucopolysaccharidoses in Northern Ireland. None of the patients had attended a cardiologist before the study. The main echocardiographical findings were thickening of the interventricular septum and left ventricular posterior wall in the absence of ECG evidence of ventricular hypertrophy. Moreover, reduced QRS voltages were present in the majority of the patients (77%) and some had reduced shortening fraction (33%). These findings suggest an infiltrative cardiomyopathy owing to mucopolysaccharide deposition as a cause of the cardiac thickening rather than true ventricular hypertrophy. Thickening of the mitral valve was present in one case and thickening of the aortic valve in two cases. Involvement of the other heart valves was minimal and aortic valve disease was not found in any of the cases of Morquio's disease type A.

In conclusion, the clinical, ECG, and chest x ray findings and echocardiographical evidence for valvular involvement were significantly less than in other studies. Hence, the incidence of clinically significant cardiovascular disease in patients with mucopolysaccharidosis has probably been overestimated.

For many years it has been recognised that the cardiovascular system is involved in the mucopolysaccharidoses (MPS). The main abnormalities found at necropsy were valvular with nodular fibrous thickening most commonly affecting the mitral valve (MV) followed by the tricuspid (TV), aortic (AV),

and pulmonary (PV) valves in decreasing order of frequency. Cardiac hypertrophy, short thickened chordae tendineae, and gross narrowing of the coronary arteries were also seen in many cases.¹⁻⁴

Valvular insufficiency has also been shown by cardiac catheterisation studies.³ Other authors^{5, 6} have reported a high incidence of ECG changes, the most common being a prolonged QT interval, although right ventricular hypertrophy (RVH), left ventricular hypertrophy (LVH), and shortened PR interval have also been described. Several studies⁷⁻¹⁰ and case reports¹¹⁻¹⁴ have presented the echocardiographical findings in various types of MPS. The most common abnormality detected was thickening of the MV with multiple MV echoes and in a few cases thickening of the AV and TV. Many cases also showed thickening of the interventricular septum (IVS) and left ventricular posterior wall (LVPW).

This study was undertaken to assess the patients from a cardiological point of view since they represented an unbiased sample. They were ascertained in the course of a genetic and epidemiological study of the mucopolysaccharidoses in Northern Ireland by one of the authors (JN).¹⁵ None of the patients had symptoms of cardiovascular disease and none had been attending a cardiologist before the study.

Patients and methods

Twenty-two cases of mucopolysaccharidosis were found to be alive and living in Northern Ireland at the time of the study. These comprised two MPS IH, three MPS IH/S, one MPS IIA, one MPS IIB, three MPS IIIA, one MPS IIIB, and 11 MPS IVA. Ascertainment was from four main sources: hospital consultant records; records of the screening laboratory for urinary mucopolysaccharides; the diagnostic indexes of the Department of Medical Genetics, The Queen's University of Belfast, The Royal Victoria Hospital, Belfast, and The Royal Belfast Hospital for Sick Children; and files of the Hospital Activity Analysis (a record of admissions to the majority of hospitals in Northern Ireland maintained by the Department of Health and Social Services).

A total of 36 cases was ascertained for the period 1958 to 1985 but 14 cases were dead and in most of these it was not possible to determine from the available hospital records and death certificates the precise cause of death. In the majority of cases a

Department of Medical Genetics, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB.

J Nelson, M D Shields, H C Mulholland

Department of Paediatric Cardiology, Royal Belfast Hospital for Sick Children, Falls Road, Belfast BT12 6BE.

J Nelson, M D Shields, H C Mulholland

Correspondence to Dr Nelson, Staff Specialist in Clinical Genetics, Westmead Hospital, Westmead, Sydney, NSW 2145, Australia.

Received for publication 10 April 1989.

Revised version accepted for publication 2 August 1989.

Figure 1 Height of R wave in lead V_6 (mm) v age.

necropsy was not performed. Consequently it was decided to confine the study to all patients who were alive and living in Northern Ireland at the time of the cardiovascular assessment. The Northern Ireland population is essentially a static one and lends itself well to epidemiological studies. It was felt that the patients ascertained represented the vast majority of patients with mucopolysaccharidosis who were alive and living in Northern Ireland at the time of the study. All cardiac investigations were carried out at the Department of Paediatric Cardiology, Royal Belfast Hospital for Sick Children.

Patient diagnosis was confirmed by two dimensional electrophoresis of urinary glycosaminoglycans by a modification of the method used for amniotic fluid glycosaminoglycans¹⁶ and by enzyme assay on leucocytes or fibroblasts as appropriate.

Each patient underwent a full assessment of the cardiovascular system, which included a full clinical examination, a 12 lead ECG, and chest x ray. M mode, two dimensional (2D), and pulsed Doppler echocardiographical examinations were performed using an Advanced Technology Laboratories (ATL) Mark 600 series duplex scanner and 3.0 or 5.0 MHz transducers as appropriate. If satisfactory imaging could not be obtained sedation was given. Measurements of IVS and LVPW thickness at end diastole, LV end diastolic dimension (LVEDD), and LV end systolic dimension (LVESD) were made from leading

edge to leading edge¹⁷ at representative cuts in the M mode record. In all cases two measurements of each parameter were made, the mean taken, and the result rounded to the nearest 0.5 mm. The shortening fraction (SF) was calculated from the formula:

$$SF = \frac{LVEDD - LVESD}{LVEDD} \times 100\%.$$

The SF is a useful measure of the quality of LV contraction and makes no assumptions about ventricular size or shape in contrast to the estimation of ejection fraction. A reduced value for SF implies poor LV function.

Standard ECG and echocardiographical normal ranges were used.¹⁸⁻²¹ The 2nd, 50th, and 98th centiles in fig 1 are from Davignon *et al.*¹⁸ Voogd *et al.*²⁰ provided 5th and 95th centiles for various echocardiographical parameters for males and females separately. For simplicity, the centiles shown in figs 2 to 4 are the mean centiles for males and females. For example, the 5th centile shown is the mean of the 5th centile for males and the 5th centile for females. This approximation does not appreciably alter the analysis of the results, but leads to easier interpretation of the figures. The 3rd and 97th centiles for SF shown in fig 5 are from Feigenbaum.²²

Figure 2 IVS thickness (cm) *v* body weight (kg).

Results

CLINICAL FINDINGS

Apart from a soft ejection systolic murmur found in six patients nothing else of note was found on clinical examination. Because of problems with cooperation, blood pressure was recorded in only 16 of the 22 patients. This was found to be raised in three (19%).

CHEST X RAY FINDINGS

Ten patients had a cardiothoracic (CT) ratio on chest x ray greater than 50% but none was grossly increased and cardiac contour and pulmonary vascularity were normal in all cases. There was no evidence of intracardiac calcification in any of the chest x rays in the series.

ECG FINDINGS

Ventricular hypertrophy was assessed with reference

Figure 3 LVPW thickness (cm) *v* body weight (kg).

to the R and S waves in leads V_1 and V_6 , the (R+S) amplitude in lead V_4 , and q waves greater than 3 mm in lead V_6 . All these measurements concurred, but for simplicity only the height of the R wave in V_6 is shown in fig 1 and table 1 for all cases. One patient (case 1) showed evidence of borderline LVH. All the other patients apart from case 16 had QRS voltages below the 50th centile and in some cases below the 2nd centile (fig 1). Three patients (cases 8, 13, and 14) had a prolonged QT_c interval. One patient (case 3) had a prolonged PR interval indicating first degree heart block and a QRS duration above the 98th centile. There was no evidence of a conduction defect in any other patient.

ECHOCARDIOGRAPHICAL FINDINGS

Fig 2 shows IVS thickness plotted against body weight and fig 3 shows LVPW thickness against body weight for each patient. The main findings were thickening of the IVS in 13 of 21 patients (62%) and LVPW in 11 of 21 patients (52%). In one patient (case 13) the IVS and LVPW could not be visualised because of gross pectus carinatum.

Fig 4 shows the LVEDD and LVESD plotted

Figure 4 LVEDD and LVESD (cm) v body weight (kg).

Figure 5 Shortening fraction (%) v body weight (kg).

against body weight. The LVEDD was above the 95th centile in two cases (cases 3 and 7) and below the 5th centile in seven cases (cases 4, 5, 6, 9, 10, 12, and 19). The LVESD was above the 95th centile in three cases (cases 3, 11, and 22) and below the 5th centile in two cases (cases 10 and 19).

The results for SF are shown in fig 5. The majority of the values are distributed around the 50th centile, but seven of the patients (33%) gave values below the 3rd centile (cases 1, 4, 9, 11, 12, 21, and 22).

Multiple mitral valve echoes were seen on M mode echocardiography in four patients (cases 1, 2, 10, and 20) but thickened MV leaflets were confirmed in only one of these patients (case 20) on the 2D image. The multiple mitral echoes seen in case 10 were thought to result from mitral valve prolapse. In case 4 thickening was observed behind the MV consistent with calcification of the MV annulus. Two cases (cases 6 and 7) showed thickening of the AV on 2D echocardiography. Doppler echocardiography confirmed a mild aortic stenosis (gradient 10 mmHg) with some regurgitation in case 6. In addition, minimal mitral regurgitation was also noted. Doppler examination in case 7 confirmed a mild AV gradient (13 mmHg) with minimal regurgitation of the PV. The only other abnormal findings by Doppler were minimal mitral regurgitation (case 8), minimal pulmonary regurgitation (case 18), and mild tricuspid regurgitation (case 19). Despite the appearance of the MV in case 20, no confirmation of stenosis by Doppler was obtained. None of the patients studied had a pericardial effusion.

Discussion

The fact that the patients were ascertained as part of an epidemiological and genetic study into the mucopolysaccharidoses in Northern Ireland,¹⁵ and none was attending a cardiologist before the study, may explain the paucity of clinical findings. Other authors have confined their investigations to patients who had been referred for cardiovascular assessment^{7 10 14} and many of these patients already had symptoms and signs of cardiovascular disease. Thus they represent a biased sample of patients. In addition, many authors do not specify how their cases were ascertained.^{5 8}

Thirteen patients (62%) had thickening of the IVS and 11 (52%) showed thickening of the LVPW, but only one patient had borderline LVH and, in general, the QRS voltages were below the 50th centile (fig 1). The apparently contradictory findings of IVS and LVPW thickening on echocardiography with lack of evidence for ventricular hypertrophy on ECG can be explained if one assumes that the cardiac wall thickening is the result of deposition of mucopolysaccharides rather than of true cardiac hypertrophy. In this situation the QRS voltages would be expected to be small since the mucopolysaccharide material is likely to be electrically non-conducting. In true cardiac hypertrophy, where the ventricular wall is thickened because of increased cardiac workload, the thickening is the result of hypertrophy of the individual muscle fibres which are electrically active during ventricular depolarisation. Thus, in true hypertrophy, the QRS voltages are likely to be large whereas in the case of ventricular thickening owing to deposition of abnormal material they are likely to be small. Against this hypothesis is the finding of very high voltage QRS complexes in glycogen storage

disease type II (Pompe's disease). Presumably infiltration of the heart by glycogen has a different effect on ventricular depolarisation compared to mucopolysaccharide deposition.

An additional factor is that the distance from the chest surface to the heart chambers may be increased in these patients since many have an increased anteroposterior diameter. Indeed, in case 13 the IVS and LVPW could not be visualised because of gross pectus carinatum. Furthermore, mucopolysaccharide material could deposit in the tissues between the heart and the ECG surface electrodes and this could also contribute to reduced QRS voltages.

There was more asymmetrical thickening in our patients compared with other series. The IVS/LVPW ratio varied from 0.8 to 2.4 with a mean of 1.3 (table 1). For example, Johnson *et al*⁷ found the thickening to be symmetrical in all of their cases in which it was present (80%) and Tada *et al*¹⁰ found that the IVS/LVPW ratio only varied between 0.9 and 1.1 in their six cases. Similarly, Salazar *et al*⁹ found the ratio varied between 1.0 and 1.2 in their four cases of MPS II. The reason for such a discrepancy is unclear.

Seven of our patients (33%) had low values of SF suggesting poor LV function. This can be explained by a combination of an infiltrative cardiomyopathy and coronary artery occlusive disease both resulting from mucopolysaccharide deposition.

Three patients had a prolonged QT_c interval. One patient (case 3) had a prolonged PR interval and a QRS duration above the 98th centile. First degree heart block has also been reported in other studies.^{5 8} The majority of the QRS voltages were below the 50th centile (fig 1) but otherwise the ECGs in our study were within normal limits and our ECG findings were

Table 1 Data for figures 1 to 5.

Case	Age		Weight (kg)	R wave in lead V ₆ (mm)	IVS thickness (cm)	LVPW thickness (cm)	IVS/LVPW	LVEDD (cm)	LVESD (cm)	SF (%)
	Y	Mth								
1	0	4	4.5	20.0	0.60	0.50	1.2	2.50	1.80	28
2	1	2	11.5	10.0	1.00	0.55	1.8	3.50	2.20	37
3	4	7	17.8	10.0	0.85	0.80	1.1	4.40	2.80	36
4	16	10	41.0	11.0	1.00	1.00	1.0	3.80	2.80	26
5	20	8	55.5	7.0	1.00	1.00	1.0	3.80	2.70	29
6	2	7	14.5	5.0	1.20	0.50	2.4	3.00	2.00	33
7	13	8	28.5	8.0	0.60	0.75	0.8	4.75	2.80	41
8	5	11	19.1	8.0	0.75	0.50	1.5	4.00	2.40	40
9	6	0	28.0	5.0	1.30	1.00	1.3	3.30	2.50	24
10	10	4	21.4	6.0	0.85	0.60	1.4	3.20	1.85	42
11	13	3	38.5	8.0	1.00	0.75	1.3	4.70	3.70	21
12	0	8	9.9	8.0	0.80	0.50	1.6	2.60	2.00	23
13	5	2	13.6	8.5	—	—	—	—	—	—
14	6	6	20.4	12.0	0.80	0.60	1.3	4.00	2.60	35
15	6	1	20.2	7.5	0.65	0.75	0.9	3.50	2.20	37
16	7	9	21.2	20.0	0.80	0.75	1.1	3.90	2.40	38
17	10	5	34.1	10.0	0.80	0.70	1.1	4.00	2.30	43
18	13	11	37.8	12.0	0.75	0.60	1.3	4.00	2.50	38
19	14	0	19.3	10.0	0.80	0.70	1.1	2.90	1.80	38
20	12	1	23.0	10.0	0.70	0.70	1.0	3.50	2.20	37
21	14	2	46.2	13.0	0.80	0.80	1.0	4.20	3.15	25
22	36	7	26.0	2.0	0.80	0.60	1.3	3.75	3.00	20

Table 2 Summary of findings according to MPS type.

Cases	Type of MPS	Clinical findings	ECG	Echocardiography
1-2	MPS IH Hurler's syndrome	Ejection systolic murmur grade 1/6 LSE (case 2)	Borderline LVH (case 1)	Multiple MV echoes (case 1, 2)
3-5	MPS IH/S Hurler/Scheie syndrome	Ejection systolic murmur grade 1/6 LSE (case 3)	P duration at upper limit, prolonged PR, QRS duration above 98% (case 3)	Thickened MV annulus (case 4)
6	MPS IIA Hunter's syndrome (severe)	Heart sounds normal	Table 1	Thickened AV, mild AS and AR, minimal MR
7	MPS IIB Hunter's syndrome (mild)	Ejection systolic murmur grade 2/6 4th LICS	Table 1	Thickened AV, mild AS, minimal PVR
8-10	MPS IIIA Sanfilippo type A	Heart sounds normal	QT _c prolonged (case 8)	Minimal MR (case 8), multiple mitral echoes and MV prolapse (case 10)
11	MPS IIIB Sanfilippo type B	Ejection systolic murmur grade 1/6 4th LICS	Table 1	Table 1
12-22	MPS IVA Morquio's disease type A	Ejection systolic murmur grade 2/6 2nd LICS (case 13) and LSE (case 19)	QRS duration 0.08 sec (case 13, 16). QT _c prolonged (case 13, 14)	Small ASD secundum (case 12, 13). Minimal PVR (case 18), mild TR (case 19), slight MV thickening and multiple MV echoes (case 20)

LSE=left sternal edge; LVH=left ventricular hypertrophy; MV=mitral valve; AV=aortic valve; AS=aortic stenosis; AR=aortic regurgitation; MR=mitral regurgitation; PVR=pulmonary regurgitation; LICS=left intercostal space; TR=tricuspid regurgitation; ASD=atrial septal defect.

much less striking than those described by other authors.⁵⁻⁸ Again the difference in the findings between our study and other studies may be because of an ascertainment bias that is present in other series.

In our series only six of the 21 patients showed multiple echoes or evidence of valvular thickening (cases 1, 2, 6, 7, 10, and 20) on M mode and 2D echocardiography. However, Johnson *et al*⁷ using M mode echocardiography only found that all five of their patients showed multiple MV echoes suggesting thickening of the anterior and posterior MV leaflets and considered that multiple valvular echoes were a frequent and characteristic finding in the mucopolysaccharidoses. In our series evidence of valvular involvement is, in general, less than other authors have described on the basis of similar investigations. Aortic valve disease, in particular aortic regurgitation, is commonly cited^{23, 24} as a complication of Morquio's disease. However, none of our 11 Morquio type A (MPS IVA) cases showed evidence of aortic valve disease. In case 4 (MPS IH/S), the echocardiogram suggested calcification of the mitral valve annulus but this was not confirmed on chest x ray. A very similar case was described by Johnson *et al*⁷ with the calcification again not being confirmed radiologically. It is probable that these findings result from mucopolysaccharide deposition within the valve ring.

Other authors^{3, 5} have reported raised blood pressure in MPS patients, the aetiology of which is unclear. Krovetz and Schiebler⁵ suspected a combination of chronic hypoxia and narrowing of the systemic arteries by plaques.

Since many authors have confined their investigations to a biased sample of patients it is probable that the extent of cardiovascular involvement in the mucopolysaccharidoses has been overestimated.

However, although our patients ranged in age from 4 months to 36 years the age range in the MPS IH (Hurler) patients was only 4 months to 1 year 2 months. Similarly the age of the MPS IIA (Hunter, severe) patient was only 2 years 7 months. On the other hand the MPS IH/S (Hurler/Scheie) patients ranged from 4 years to 20 years, the MPS III (Sanfilippo) patients from 5 years to 13 years, and the MPS IVA (Morquio type A) patients from 8 months to 36 years. Thus the paucity of cardiac abnormalities might be a reflection of the relatively young age of some of our groups of patients, but it is unlikely that this would provide a full explanation for the paucity of findings in all cases. Without doubt these patients develop progressive valvular involvement so that at necropsy marked valvular thickening may be present. However, this does not mean that the majority of patients will have symptoms or signs of cardiovascular

disease or will die from cardiac causes. A prospective study of all patients with MPS would give a truer incidence of clinically significant cardiovascular disease than isolated case reports. In addition, the rate of diastolic filling and LV compliance may be more sensitive indicators of muscle dysfunction and their assessment might yield further information on mucopolysaccharide deposition within the myocardium.

We thank the following: Professor N C Nevin, Department of Medical Genetics, Belfast City Hospital for allowing free access to the patients of the Department; Mrs Jayne Rogers, Chief Physiological Measurement Technician, Cardiology Department, Royal Belfast Hospital for Sick Children, for assistance in performing the echocardiography and the ECGs; Dr Brian Craig, Consultant Paediatric Cardiologist, Royal Belfast Hospital for Sick Children; Dr Norman Campbell, Consultant Cardiologist, Royal Victoria Hospital, Belfast and Dr Jim Ramsey, Consultant Paediatric Cardiologist, Princess Margaret Hospital for Children, Perth, Western Australia for helpful advice and comments; and Dr Paul Thomas, Consultant Radiologist, Royal Belfast Hospital for Sick Children for review of the chest x rays.

- Lindsay S. The cardiovascular system in gargoylism. *Br Heart J* 1950;12:17-32.
- Emanuel RW. Gargoylism with cardiovascular involvement in two brothers. *Br Heart J* 1954;16:417-22.
- Krovetz LJ, Lorincz AE, Schiebler GL. Cardiovascular manifestations of the Hurler syndrome. Hemodynamic and angiographic observations in 15 patients. *Circulation* 1965;31:132-41.
- Renteria VG, Ferrans VJ, Roberts WC. The heart in the Hurler syndrome. Gross, histologic and ultrastructural observations in five necropsy cases. *Am J Cardiol* 1976;38:487-501.
- Krovetz LJ, Schiebler GL. Cardiovascular manifestations of the genetic mucopolysaccharidoses. *Birth Defects* 1972;8(5):192-6.
- Fuster Siebert M, Caamaño Mata JM, Fraga Bermúdez JM, Cousselo Sánchez JM. Sanfilippo syndrome and shortened PR. *Med Clin (Barc)* 1982;79:387-8.
- Johnson GL, Vine DL, Cottrill CM, Noonan JA. Echocardiographic mitral valve deformity in the mucopolysaccharidoses. *Pediatrics* 1981;67:401-6.
- Schieken RM, Kerber RE, Ionasescu VV, Zellweger H. Cardiac manifestations of the mucopolysaccharidoses. *Circulation* 1975;52:700-5.
- Salazar J, Ferrández A, Felipe J, García MD. El ecocardiograma mitral en el síndrome de Hunter. *An Esp Pediatr* 1979;12:591-6.
- Tada A, Tanaka A, Yasuda M, et al. Cardiac manifestation of the mucopolysaccharidoses: periodical echocardiographic evaluation in six cases. *J Cardiatr* 1983;13:407-23.
- Ireland MA, Rowlands DB. Mucopolysaccharidosis type IV as a cause of mitral stenosis in an adult. *Br Heart J* 1981;46:113-5.
- Vergassola R, Sansoni M, Vanelli P, Testa O. Cardiac changes in the mucopolysaccharidoses. *Minerva Cardioangiol* 1982;30:11-14.
- Oliver J, Garcia Fernandez F, Sotillo J, et al. Mitral insufficiency and severe aortic stenosis in a patient with Hunter's syndrome. *Rev Esp Cardiol* 1982;35:465-9.
- Hada Y, Lee Y, Sakamoto T, et al. Echocardiographic manifestations of the heart in the Hunter syndrome: report of a case. *J Cardiatr* 1982;12:1043-53.
- Nelson J. *The mucopolysaccharidoses in Northern Ireland. A clinical, genetic and biochemical study*. MD thesis, The Queen's University of Belfast, 1986.
- Mossman J, Patrick AD. Prenatal diagnosis of mucopolysaccharidosis by two-dimensional electrophoresis of amniotic fluid glycosaminoglycans. *Prenat Diagn* 1962;2:169-76.
- Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978;58:1072-83.
- Davignon A, Rautaharju P, Boisselle E, Soumis F, Megelas M, Choquette A. Normal ECG standards for infants and children. *Pediatr Cardiol* 1979;1:123-52.
- Park MK, Guntheroth WG. *How to read pediatric ECGs*. Chicago: Year Book Medical Publishers, 1981.
- Voogd PJ, Rijsterborgh H, Van Zwieten G, Lubsen J. Percentile of echocardiographic dimensions in healthy children and young adolescents. In: Lancée C, ed. *Echocardiology. Proceedings of the Third Symposium on Echocardiology*. The Hague: Nijhoff, 1979:299-307.
- Lintermans JP, Van Dorp WG. *Differential diagnosis in pediatric echocardiography*. Berlin: Springer-Verlag, 1981.
- Feigenbaum H. *Echocardiography*. 3rd ed. Philadelphia: Lea and Febiger, 1981.
- Smith DW. *Recognizable patterns of human malformation*. 3rd ed. Philadelphia: Saunders, 1982.
- Goodman RM, Gorlin RJ. *The malformed infant and child. An illustrated guide*. Oxford: Oxford University Press, 1983.