Cardiac and ocular manifestations in Egyptian patients with mucopolysaccharidoses

R.M. Shawky,[1] M.T. Abd El-Monim,[2] A.A. El-Sebai [3] and S.M. El-Sayed[1]

المظاهر القلبية والعينية لدى المصريين المصابين بداء عديدات السكريدات المخاطية

رباح محمد شوقي، محمود طارق عبد المنعم، عزيزة أحمد الساعي وسلاف محمد السيد

خلاصة: تم تقييم المظاهر القلبية والعينية لدى 21 مريضاً يشتبه سريرياً (إكلينيكياً) بإصابتهم بداء عديدات السكريدات المخاطية، وبعد إجراء الرحلان الكهربي لمركبات الأمينوغليكان في البول تم استبعاد ثلاثة مرضى بسبب عدم تطابق نتائجهم مع أي نوع معروف من أنواع داء عديدات السكريدات المخاطية. وقد أظهر الفحص بالصدي القلبي موجودات مرضيّة لدى 11 مريضاً (61.1٪) وكان الصمام المترالي هو الأكثر إصابة لدى 7 مرضى (38.9٪)، إذ ظهر هذا الصمام لديهم متكثفاً، وظهر لدى 6 من المرضى قلس (عودة الدم) عبر الصمام المترالي. ولوحظت كثافات قرنية لدى 3 مرضى (16.7٪) مع ازدياد متفاقم في الضغط داخل المقلة لدى مريض واحد (5.6٪) ورذمة حليمة العصب البصري في الجانبين لدى مريضين (11.1٪) وضمور باكر للعصب البصري في مريض واحد (5.6٪) بفحص قعر العين.

ABSTRACT Cardiac and ocular manifestations were evaluated in 21 patients clinically suspected of mucopolysaccharidosis. After electrophoresis analysis of urinary glycoaminoglycans, 3 patients were excluded because their results did not correlate with any known type of mucopolysaccharidosis. Echocardiography revealed abnormal findings in 11 patients (61.1%). The mitral valve was the most commonly affected valve; 7 patients (38.9%) had thickened mitral valve and 6 had mitral regurge. Corneal opacities were found in 3 patients (16.7%) and progressive increase in intraocular pressure in 1 patient (5.6%), while fundus examination showed early optic atrophy in 1 patient (5.6%) and bilateral papilloedema in 2 patients (11.1%).

Manifestations cardiaques et oculaires chez des patients égyptiens atteints de mucopolysaccharidose

RESUME Les manifestations cardiaques et oculaires ont été évaluées chez 21 patients cliniquement suspects de mucopolysaccharidose. Après analyse par électrophorèse des glycosaminoglycanes urinaires, 3 patients ont été exclus car leurs résultats ne correspondaient à aucun type connu de mucopolysaccharidose. L'échocardiographie a révélé des anomalies chez 11 patients (61,1%). La valve mitrale était la valve la plus couramment touchée, avec un épaississement de la valve mitrale retrouvé chez 7 patients (38,9 %) et une régurgitation mitrale chez 6 patients. On a trouvé des opacités de la cornée chez 3 patients (16,7 %) et une augmentation progressive de la pression intraoculaire chez 1 patient (5,6 %) ; l'examen du fond de l'œil a montré une atrophie optique précoce chez 1 patient (5,6 %) et des œdèmes papillaires bilatéraux chez 2 patients (11,1 %).

[1]*Genetics Unit, Department of Paediatrics;* [2]*Department of Paediatrics;* [3]*Department of Clinical Pathology, Ain Shams University, Cairo, Egypt*

Received: 23/01/01; accepted: 17/04/01

Introduction

The mucopolysaccharidoses (MPS) are a group of lysosomal storage diseases, each of which is produced by an inherited deficiency of an enzyme involved in the degradation of acid mucopolysaccharides [now called glycosaminoglycans GAGs)]. Incompletely degraded GAGs accumulate in multiple organ systems leading to progressive worsening of clinical manifestations, such as coarse facies, dysostosis multiplex and heart disease. The MPS are inherited as autosomal recessive traits with the exception of the two subtypes of Hunter disease, which show X-linked inheritance [*1*]. Cardiovascular and ocular manifestations have special importance. Cardiac abnormalities, especially valvular lesions, are relatively common and are considered the most life-threatening complications [2]. Ocular manifestations include progressive corneal clouding, glaucoma, optic atrophy and retinal degeneration [*3*].

The aim of this work was to study the cardiac and ocular abnormalities in Egyptian patients with MPS to ensure early diagnosis and proper treatment of these complications. At the same time we evalu ated different methods of measuring urinary GAGs, and hence identifying different types of MPS.

Methods

The study was conducted on 21 patients attending the Genetics Unit, Department of Paediatrics, Ain Shams University. Patients were diagnosed with MPS according to the clinical features described by Neufeld and Muenzer in 1995 [*4*]. These features are shared by different types of MPS and include a chronic and progressive course of the condition, multisystem involvement, organomegaly, dysostosis multiplex and abnormal facies with or without mental retardation.

All patients underwent the following procedures.

- Full history with special emphasis on developmental history, cardiovascular system (CVS) and ocular symptoms.
- Thorough clinical examination, including examination of the eyes, CVS, abdomen, skull and skeleton.
- The following investigations:
  - Urine screening by Berry spot test (toluidine blue test) [*5*];
  - Determination of urinary total GAGs with Alcian blue 8GX [*6,7*];
  - Characterization and scanning of urinary GAGs by electrophoresis [*8*];
  - Radiological examination of chest and heart;
  - 12-lead standard electrocardiogram (ECG);
  - Echocardiography using ACUSON computed sonography system (model 128XP5), including M-mode, two-dimensional echocardiography, pulsed Doppler, continuous wave Doppler and colour flow mapping;
  - Ophthalmological examination including slit-lamp examination, fundus examination, and measurement of intraocular pressure.

As a comparison group, 10 apparently normal children matched for age and sex were included in the study.

Results

The study was conducted on 21 patients who from clinical evidence were suspected of having MPS. There were 10 males (47.6%) and 11 females (52.4%), with an age range of 2–15 years (mean 7 ± 3.95

years). A history of other affected siblings was found in 5 families.

The results of the measurement of total GAGs in urine in relation to creatinine concentration are shown in Table 1.

The results of the toluidine blue test and urine electrophoresis are shown in Table 2. The toluidine blue test was positive in 17 cases (81.0%) and negative in 4 cases (2 of which were clinically MPS type IV and 2 were clinically MPS type III). Of these 4 cases, 2 were proven to be MPS type III and one MPS type IV by urine electrophoresis (confirming the clinical diagnosis; only one case was negative by electrophoresis. Three of the cases were excluded from the study because their results did not correspond to that of any known type of MPS (Table 3).

Abnormal ECG findings were noted in 7 patients (38.9%) (Table 4). Echocardiography revealed abnormal findings in 11 patients (61.1%): 2 patients with MPS type I, 3 with MPS type III, 2 with MPS type IV and 4 with MPS type VI (Table 5. Figures 1 and 2). The mitral valve was the most commonly affected valve. Mitral regurge of grade 1/4 to 2/4 was found in 6 patients (i.e. 54.5% of those with cardiac abnormalities). One patient with MPS type IV had a significantly dilated aorta in addition to aortic regurge grade 2/4.

The ocular findings of the patients studied are shown in Table 6. In all, 6 patients (33.3%) showed some abnormality: 1 with MPS type I, 1 with MPS type II, 2 with MPS type III, and 2 with MPS type VI.

Discussion

We evaluated different diagnostic techniques for MPS in the patients studied. The toluidine blue test was used as an initial screen for MPS. The results showed that the test correctly diagnosed 76.2% of the patients, with 9.5% false positives and 14.3% false negatives. These results and similar observations reported by de Jong et al. [9] indicate that the toluidine blue test cannot be considered a reliable test for the diagnosis of MPS. In addition, it has been reported that urine specimens from patients with MPS types III and IV usually give false negative results [10], while other studies have found that patients with gangliosidosis [11] or multiple sulfatase deficiency [12] may give false positive results. On the other hand, the total GAGs in urine were significantly higher in patients than in controls, which concurs with other studies [6]. Urine electrophoresis was shown to be a sensitive and reliable method for diagnosis of different types of MPS, which is in agreement with the study of de Jong et al. [9].

CVS abnormalities were detected in 11 (61.1%) of the studied cases. These abnor-

Table 1 **Total glycosaminoglycans in the urine of patients and controls**

Group	Glycosaminoglycans (mg %)			Creatinine (mg/mmol)		
	Range	Mean	*s*	Range	Mean	*s*
Patients	28.19–79.29	52.7	15	7.07–32.85	12.8	6.6
Controls	13.51–27.52	18.9	4	1.75–6.14	2.82	1.4
P-value	< 0.05			< 0.05		

Table 2 **Results of toluidine blue test and urine electrophoresis in relation to clinical diagnosis**

Clinical diagnosis	Toluidine blue	Electrophoresis DS	HS	KS	CS	Type identified by electrophoresis
IV	Positive	–	–	+	+	IV
III	Positive	–	+	–	–	III
III	Positive	–	+	–	–	III
IV	Negative	–	–	+	+	IV
I	Positive	+++	+	–	–	I
III	Negative	–	+	–	–	III
IV	Positive	–	–	+	+	IV
III	Negative	–	+	–	–	III
IV	Negative	–	–	–	–	Negative[a]
I or II	Positive	+	+	–	–	II
VI	Positive	+	–	–	–	VI
VI	Positive	+	+	–	+	VII
I or II	Positive	+++	+	–	–	I
IV	Positive	–	–	+	+	IV
VI	Positive	+	–	–	–	VI
VI	Positive	–	+	–	+	?[a]
VI	Positive	+	–	–	–	VI
VI	Positive	+	–	–	–	VI
III	Positive	+	–	+	–	?[a]
VI	Positive	+	–	–	–	VI
VI	Positive	+	–	–	–	VI

DS = dermatan sulfate, HS = heparan sulfate, KS = keratan sulfate, CS = chondrotin sulfate.

+++ indicates more dermatan than keratan

[a]These patients were excluded from the study as the electrophoresis results did not correlate with any known type of mucopolysaccharidosis.

malities were detected clinically and by ECG as well as echocardiography: ECG abnormalities in MPS were reported in 7 patients (38.9%). These results are in agreement with those of Schieken et al. [*13*]. The reported conduction defects in both studies may be attributed to the infiltration of the conduction system by GAGs [*14*], and focal infiltration of sinoatrial and atrioventricular nodes by fibroelastic tissues and Hurler cells [*15*].

Mitral regurge was the commonest abnormality detected in our patients, both clinically and by echocardiography (n = 6,

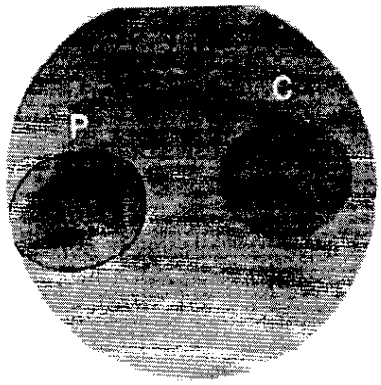

Figure 1 **Positive toluidine blue test (P: patient; C: control)**

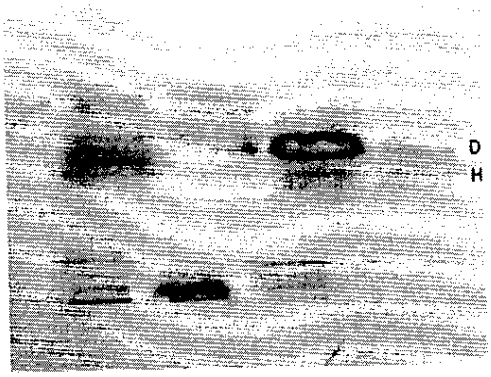

Figure 2 **Urine electrophoresis for three patients; standards for heparan (H) and dermatan (D) sulfate (from left to right)**

33.3%). This observation is in agreement with the study of Johnson et al. [*16*]. Mitral regurge is most likely caused by an accumulation of GAGs in the valve leaflets, causing thickening of the valve and the chordae with subsequent dysfunction of the papillary muscle and ultimately mitral regurge [*13*]. Mitral regurge was commoner in MPS types I (2 patients) and VI (3 patients). This is in agreement with the findings of Wippermann et al. [*17*], Gross et al. [*18*] and Pyeritz et al. [*19*]. On the other hand, aortic regurge was detected in MPS types I (1 patient) and IV (2 patients). This is again consistent with reports by other authors [*14,19*].

Absence of significant cardiomegaly in our study may be explained by the fact that

Table 3 **Different types of mucopolysaccharidosis in the group studied according to clinical impression and electrophoresis**

Mucopolysaccharidosis type	Clinical impression ($n = 21$)		Electrophoresis ($n = 18$)	
	No.	%	No.	%
I	1	4.8	2	11.1
II	–	–	1	5.6
I or II	2	9.5	–	–
III	5	23.8	4	22.2
IV	5	23.8	4	22.2
VI	8	38.1	6	33.3
VII	–	–	1	5.6

Table 4 **Electrocardiograph abnormalities in the patients in relation to the mucopolysaccharidosis type**

ECG abnormality	Number of patients affected	Mucopolysaccharidosis type
Premature ventricular contractions	1	VI
Incomplete (right) bundle branch block	1	II
	1	VI
Right ventricular enlargement	2	VI
Left ventricular enlargement	1	VI
Biventricular enlargement	1	VI

nearly all our patients had mild valvular involvement (grade 1/4 or 2/4 regurgitation) as proved by echocardiography, which was not severe enough to cause significant chamber enlargement. Although annular calcification of the mitral valve usually occurs in patients with MPS type I Hurler/Scheie (H/S) [*14*], none of our patients was of this type.

Valve stenosis was not observed in any of our patients. Again, this may be because mitral valve stenosis is usually found in patients with MPS type I H/S [*14*]. Aortic stenosis has been described in patients with MPS type I S and MPS VI over 60 years of age [*2*], while all of our patients were under 16 years. Masuda et al. suggested that dermatan sulfate and chondroitin sulfate play an important role in the sclerosis and calcification of cardiac valves [*2*]. They also reported that levels of hyaluronic acid found in sclerotic valves are low, which may cause a reduction in valve flexibility as a result of the attenuation of the water-binding capacity of the tissue.

Pulmonary hypertension was found only in 2 of our patients with MPS type III (11.1%). Pyeritz stated that pulmonary hypertension is found in MPS patients but did not specify the type most commonly involved [*19*].

Coronary narrowing was found in 2 patients (11.1%), one with MPS I (affecting both coronaries); the second of MPS type IV with involvement of the right coronary only. Brosius and Roberts found extensive coronary narrowing in 80% of patients with MPS [*20*]. They stated that patients with Hurler syndrome usually have diffuse and severe coronary luminal narrowing, produced primarily by a combination of Hurler cells, fibrous tissue and GAGs. It is usually asymptomatic because young children are unable to communicate their pain [*21*]. However, coronary involvement may be severe enough to produce myocardial ischaemia and infarction [*22*].

In the present study, systemic hypertension was not found in any of our patients. This is in contrast to what was found in the study of Taylor et al. [*21*]. They attributed hypertension in MPS to an occlusive pathology of the aorta or renal arteries and found that this is common in

Table 5 **Echocardiographic abnormalities noted in the patients studied in relation to mucopolysaccharidosis type**

Echocardiographic abnormality	Number of patients affected	Mucopolysaccharidosis type
Right ventricular enlargement	1	IV
Coronary thickening	1	I
	1	IV
Increased interventricular thickness	3	III, IV, VI
Thickened mitral valve	3	III
	2	IV
	2	VI
	1	I
Thickened tricuspid valve	1	I
Thickened aortic valve	2	I
	1	III
	1	VI
Pulmonary hypertension	2	III
Mitral regurge	2	I
	1	III
	3	VI
Tricuspid regurge	1	I
	2	III
	1	IV
	1	VI
Aortic regurge	1	I
	2	IV

patients with MPS type I. The absence of hypertension in our cases may be because they were younger than those examined by Taylor et al. and also because only 2 of our patients had MPS type I [*21*]. Comparison of our study and previous reports of the incidence of CVS abnormalities revealed marked variability. In the study of Nelson and colleagues, 4.5% of patients with MPS had thickening of the mitral valve and 9% had thickening of the aortic valve with minimal involvement of other valves [*23*]. On the other hand, Wippermann et al. found mitral valve thickening in 92.9% of their patients and aortic valve thickening in 51.1% of their patients [*17*]. The results in our study seem to lie between these two studies. Variability between different studies in the incidence of CVS abnormalities can be attributed to differences in the type

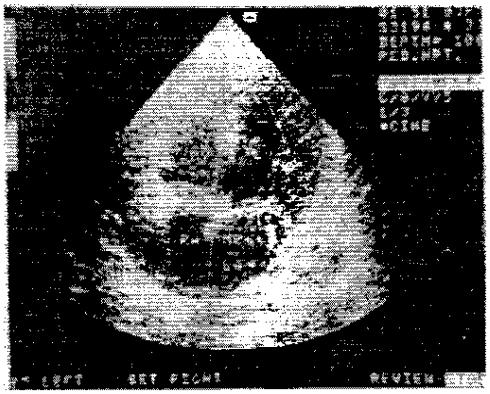

Figure 3 **Colour flow Doppler showing mitral regurge in a patient with mucopolysaccharidosis type I**

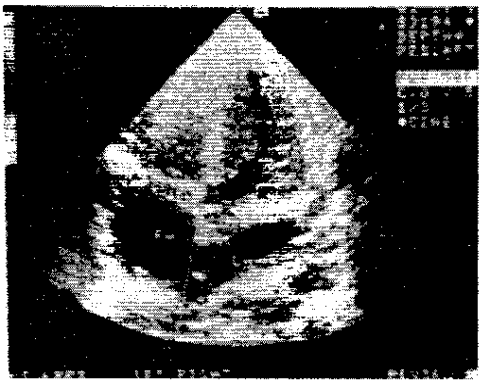

Figure 4 **Colour flow Doppler showing aortic regurge in a patient with mucopolysaccharidosis type I**

of MPS studied. Patients with MPS type IV appear to be the type least likely to develop cardiac defects, since the major GAG in this type is keratan sulfate, which is stored predominantly in the skeletal system. In other types of MPS, the major GAG is dermatan and/or heparan sulfate, which affects all other tissues. In addition, the use of colour flow echocardiography in recent studies (which can detect small or eccentric jets) can be one of the causes of the variability in the incidence of CVS abnormalities detected.

In the present study, corneal clouding was found in 1 patient (5.6%) with MPS type I and 1 patient with MPS type IV (5.6%), by oblique focal illumination. Slit-lamp examination confirmed these findings

Table 6 **Ocular findings in the patients studied in relation to mucopolysaccharidosis type**

Ocular abnormality	Number of patients affected	Mucopolysaccharidosis type
Papilloedema	2	VI
Pigmentary changes	1	III
Increased intraocular pressure (glaucoma)	1	I
Optic atrophy	1	II
Corneal clouding	1	I
	1	III
	1	VI

and also detected corneal clouding in a further patient with MPS III (5.6%). These findings are in agreement with Frangieh et al. [3] who reported that corneal clouding can be detected by oblique focal illumination in MPS types I, IV and VI, but in types II and III its detection needs a more sensitive method such as slit-lamp examination.

Glaucoma was found in one of our patients with Hurler syndrome (5.6%) who was 2 years old. Intraocular pressure was found to have increased after 9 months. This agrees with the data of Nowaczyk et al., who found that glaucoma occurs as an early complication of Hurler syndrome due to engorgement of the trabecular meshwork by GAGs with subsequent distortion and thickening of the intracellular matrix of sclera and corneas, resulting in further constriction of the anterior chamber [24]. The presence of incompletely degraded GAGs in the outflow apparatus is also thought to inhibit hyaluronidase and other enzymes involved in the maintenance of normal aqueous outflow.

Fundus examination demonstrated that papilloedema was present in 2 out of 6 patients with MPS type VI (33.3%) but with no evidence of intracranial tension (ICT), as confirmed by the normal computed tomography brain scan of both patients. These are very close to the result reported by the study of Collins et al. [1], who found that patients with MPS types I H, I H/S, VI and VII have a greater than 40% chance of developing papilloedema. The probability was less in MPS types III and II patients. It is generally accepted that disc elevation (papilloedema) and optic atrophy in MPS is secondary to increased ICT and hydrocephalus. However, Beck and Cole reported patients with MPS and papilloedema who had no signs of increased ICT or hydrocephalus [25]. Several theories of the pathogenesis of papilloedema have been proposed, all of them involving the accumulation of GAGs in various tissues. GAG accumulation in the meninges or in the dura mater causes compression of the optic nerve and papilloedema. Compression of the optic nerve axons by a markedly thickened sclera may also cause papilloedema.

Only one of our patients (5.6%) with Hunter syndrome was found to have early optic atrophy. The reason for this low percentage is the short duration of the study, as optic atrophy develops over prolonged periods of time, as found by Collins et al. [1]. Their study was conducted over 17 years and showed that optic atrophy occurs in 40% of patients with MPS types I H, I H/S, IV and VII, in less than 19.7% of patients with MPS type III and in 4.6% of patients with MPS type II.

Pigmentary retinopathy was found in one patient with MPS type III (5.6%). Frangieh et al. stated that progressive pigmentary retinopathy occurs in MPS types I, II, III and VII [3]. This was explained by the deposition of GAGs within and around blood vessels, with accumulation of the pigment within the macrophage and free in the tissue [25].

In conclusion, cardiac and ocular manifestations are common in Egyptian patients with MPS. In patients with MPS, regular cardiac examination, (ECG, echocardiography), and ophthalmology, including slit-lamp examination, fundus examination and regular measurement of the intraocular pressure, are necessary for the early detection and management of potential complications. Our results also confirm that urine electrophoresis is a simple and reliable method for the accurate detection of MPS subtypes.

References

1. Collins MZ, Traboulsi EI, Maumenee IH. Optic nerve head swelling and optic atrophy in systemic mucopolysaccharidoses. *Ophthalmology*, 1990, 97:1445– 9.
2. Masuda H et al. Aortic stenosis associated with Scheie's syndrome. Report of successful valve replacement. *Chest*, 1993, 103:968–70.
3. Frangieh GT, Lee JS, Smith RE. The cornea in systemic disease. In: Tasman W, Jaeger EA, eds. *Duane's clinical ophthalmology*. Philadelphia, Lippincott, 1992:27–38.
4. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Scriver CR et al., eds. *The metabolic and molecular basis of inherited diseases*, Vol. II, 1990:2465–94.
5. Berry HK, Spinanger J. A paper spot test useful in study of Hurler's syndrome. *Journal of laboratory and clinical medicine*, 1960, 55:136–8.
6. Whiteman P. The quantitative measurement of Alcian blue glycosaminoglycan complexes. *Biochemical journal*, 1973, 131:343–5.
7. Whiteman P. The quantitative determination of glycosaminoglycans in urine with Alcian blue 8GX. *Biochemical journal*, 1973, 131:351–7.
8. Wessler E. Analytic and preparative separation of acidic glycosaminoglycans by electrophoresis in barium acetate. *Analytical biochemistry*, 1968, 26:439–44.
9. de Jong JGN et al. Dimethylene blue-based spectrophotometry of glycosaminoglycans in untreated urine: a rapid screening procedure for mucopolysaccharidoses. *Clinical chemistry*, 1989, 35:1472 7.
10. Anderson HC, Shapira E. The mucopolysaccharidoses: Inherited disorders of connective tissue. In: Bennet C, Plum F, eds. *Cecil's textbook of medicine*, 20th ed. Philadelphia, WB Saunders Company. 1996:1118.
11. Klein M et al. Urine screening for disorders of polysaccharide metabolism. *Pediatrics*, 1969, 44:768.
12. Spranger J. The mucopolysaccharidoses. In: Rimoin DL, Connor JM, Pyeritz RE, eds. *Emery and Rimoin's principles and practice of medical genetics*, 2nd ed. New York, Churchill Livings-tone, 1996: 1797–806.
13. Schieken RM et al. Cardiac manifestations of mucopolysaccharidoses. *Circulation*, 1975, 52:700–5.
14. Pierpont MEM, Moller JH. Cardiac manifestations of genetic diseases. In: Allen HD et al., eds. *Moss and Adams' heart disease in infants, children and adolescents: including the fetus and young adult*, 5th ed. Philadelphia, Williams and Wilkins, 1995:1509–10.
15. Stephan MJ et al. Mucopolysaccharidosis I presenting with endocardial fibroelastosis in infancy. *American journal of diseases of children*, 1989, 143: 782–4.
16. Johnson GL et al. Echocardiographic mitral valve deformity in the mucopolysaccharidoses. *Pediatrics*, 1981, 67: 401–6.
17. Wippermann CF et al. Mitral and aortic regurgitation in 84 patients with mucopolysaccharidoses. *European journal of pediatrics*, 1995, 154(2):98–101.
18. Gross DM et al. Echocardiographic abnormalities in mucopolysaccharide storage diseases. *American journal of cardiology*, 1988, 61:170–6.

19. Pyeritz RE. Genetic and cardiovascular disease. In: Braunwald E, ed. *Heart disease: a textbook of cardiovascular medicine*, 4th ed. Philadelphia, WB Saunders Company. 1992:1661.

20. Brosius FC, Roberts WC. Coronary artery disease in the Hurler syndrome. Qualitative and quantitative analysis of the extent of coronary narrowing at necropsy in six children. *American journal of cardiology*, 1981, 47:649–53.

21. Taylor DB et al. Arteriopathy and coarctation of the abdominal aorta in children with mucopolysaccharidoses: imaging findings. *American journal of roentgenology*, 1991, 157:819–23.

22. Towbin J, Roberts R. Cardiovascular disease due to genetic abnormality. In: Schlant RC, Alexander RW, eds. *Hurst's the heart, arteries and veins*, 8th ed. New York, McGraw–Hill, 1994:1751.

23. Nelson J, Shield MD, Mulholland HC. Cardiovascular studies in the mucopolysaccharidoses. *Journal of medical genetics*, 1990, 27:94–100.

24. Nowaczyk MJ, Clarke JTR, Morin JD. Glaucoma as an early complication of Hurler's disease. *Archives of disease in childhood*, 1988, 63:1091–3.

25. Beck M, Cole G. Disc oedema in association with Hunter's syndrome. Ocular histopathological findings. *British journal of ophthalmology*, 1984, 68:590–4.

Note from the Editor

We would like to draw our readers' attention to the evaluation form at the end of this issue. We welcome comments from our readers, which can help us improve the EMHJ. We would appreciate it therefore if readers could kindly take the time to complete this form and return it to us.