Review Article

Early diagnosis and management of cardiac manifestations in mucopolysaccharidoses: a practical guide for paediatric and adult cardiologists

Boffi L, Russo P, Limongelli G. *Italian J Pediatrics* 2018;44(Suppl 2):122.

Background

- Mucopolysaccharidoses (MPS) are a group of hereditary disorders caused by lysosomal storage of glycosaminoglycans (GAGs) and characterised by a wide variability in phenotypes from severe fetal-neonatal forms to attenuated disease in adults.[1]
- The clinical picture generally worsens with age due to progressive storage involving mucosal tissue, upper airways and lungs, bones and joints, central and peripheral nervous system, heart, liver, eye and ear.[1]
- Cardiac storage of GAGs involves the valves, heart muscle, and vessels (particularly the coronary arteries), and can be specific in relation to different MPS types and enzyme defects.[1]
- MPS I, II and VI are those with the most severe cardiac involvement.[1]

The cardiologist is a key figure in MPS; correct interpretation of clinical and laboratory findings and of typical electrocardiography (ECG) and imaging features may help in making an early clinical diagnosis.[1]

Diagnosis

The diagnosis of MPS is based on cardiac and non-cardiac disease manifestations.[1] Red flags for the diagnosis have been proposed (Table 1, Figures 1 and 2).[1]

Family history

- Ethnic background and pedigree (i.e. consanguinity) should be considered in the diagnosis.[1] Male-to-male transmission excludes a diagnosis of MPS.[1]

Clinical examination

- Evidence of a cardiac murmur (aortic, mitral) in the presence of typical dysmorphic features (coarse face), skeletal and joint abnormalities, is highly suggestive of MPS and should be differentiated from other genetic disorders.[1]

Note: The absence of a cardiac murmur and/or one or more systemic features does not exclude the diagnosis due to the heterogeneity of the phenotype (especially in adult patients with milder forms).[1]

ECG

- ECG is mandatory in patients with MPS.[1]
- Atrioventricular blocks may be common in some specific MPS subtypes but are rarely progressive.[1]

Imaging

M-mode two-dimensional Doppler echocardiography is the gold standard for the diagnosis of cardiac involvement in MPS.[1]

- Valve damage in MPS is quite common and typical.[1]
- Intramyocardial infiltration of GAGs (pseudohypertrophy) may be present.[1]

It is important to regularly measure wall thickness, left ventricular dimensions and cardiac mass.[1]

- Endocardial fibroelastosis is a rare and serious presentation of infantile MPS.[1]

Laboratory measures

- Brain natriuretic peptide (BNP) and its precursor NT-proBNP can be considered to distinguish between cardiac and pulmonary dyspnoea (since they often coexist), and to guide cardiac therapy.[1]

Table 1: Ten-point checklist for cardiologists to suspect mucopolysaccharidosis (proposed red flags for the diagnosis of MPS)[1]

1. Family history: consanguinity and/or X-linked inheritance (female to male; no male to male transmission)	Yes/No
2. Hump/spinal column malformations	Yes/No
3. Hip dysplasia	Yes/No
4. Inguinal hernia	Yes/No
5. Respiratory infections	Yes/No
6. Facial dysmorphisms	Yes/No
7. Corneal opacity/retinitis	Yes/No
8. Valve disease (mitral/aortic)	Yes/No
9. Electrocardiography: atrioventricular block	Yes/No
10. Aortopathy/coronary artery disease	Yes/No

Children			
	 "Red"	 "Orange"	 "Yellow"
Cardiac	Valve Diseases Cardiomyopathy	ECG Abnormalities Aorthopathy	Coronary Artery Disease Fibroelastosis
Systemic	Hump/spinal column malformations Inguinal Hernia + Resp Infect + Hip dyspl	Inguinal Hernia + Hip dyspl Resp Infect + Hip dyspl Inguinal Hernia + Resp Infect	Single defects

Fig. 1 Cardiac and systemic hallmarks/flags (red, orange, yellow) for the clinical diagnosis of MPS in children. Definite diagnosis: combination of cardiac + systemic red flags; probable diagnosis: combination of cardiac + systemic orange flags; possible diagnosis: combination of cardiac + systemic yellow flags. This classification is based on expert points of view and prevalence of defects. To date, no data are available on sensitivity and specificity of single and composed clinical hallmarks of the disease. ECG - electrocardiography, dyspl - dysplasia, Resp Infect - respiratory infections[1]

Adolescents & Adults	
	 "Red"
Cardiac	Non inflammatory Aorthopathy
Systemic	Corneal opacity Retinitis

Fig. 2 Cardiac and systemic hallmarks/flags (red) for the clinical diagnosis of MPS in adolescents/adults[1]

Management

Valve disease in MPS

- Cardiological follow-up (clinical evaluation, ECG and echocardiography) should be performed yearly for mild or stable valvular disease and at least twice a year for patients with severe valvular disease with signs of suboptimal heart function.[1]
- Patients should be treated with heart failure drugs according to conventional guidelines.[1]
- Follow-up should be even more frequent (every 3 to 6 months) in patients with symptoms of heart failure to optimise drug therapy or to define a surgical indication.[1]
- A surgical intervention for valvular replacement is indicated in symptomatic patients without significant comorbidities, and for asymptomatic patients with severe valvular diseases and with evident signs of disease progression.[1]

Cardiomyopathy in MPS

- Cardiomyopathy without valvular disease is a rare presentation of very severe forms of MPS.[1] Hospitalisation is usually required to optimise pharmacological therapy and/or to support circulation in a life-threatening presentation (intravenous inotropic support).[1]
- Cardiomyopathy secondary to valvular disease is less severe, with a later onset, often requiring pharmacological treatment or, in some cases, valve replacement.[1]

Coronary artery disease in MPS

- Coronary artery disease is often clinically silent in patients with MPS.[1]
- In patients with a planned valve replacement, coronary angiography is mandatory before valve replacement, and it should be considered when a strong suspicion of ischaemic heart disease (repolarisation abnormalities, ventricular arrhythmias, progressive systolic impairment) has been raised.[1]

Aortopathy in MPS

- Aortopathy is an emerging problem in MPS patients.[1]
- Angiotensin-1 receptor blockers represent a promising therapy based on experimental studies.[1]

Conclusions

- Cardiac involvement is part of the clinical spectrum in MPS, mostly involving types I, II and VI.[1]
- Valve disease is the most common cardiac defect at disease onset, while dilated cardiomyopathy and coronary involvement are rarer.[1]
- Cardiologists should be aware of the clinical features and natural history of the disease since early diagnosis and management are important in the most severe presentations.[1]

Reference: 1. Boffi L, Russo P, Limongelli G. Early diagnosis and management of cardiac manifestations in mucopolysaccharidoses: a practical guide for paediatric and adult cardiologists. *Italian J Pediatrics* 2018;44(Suppl 2):122.

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