Cardiac involvement in mucopolysaccharidoses: effects of allogeneic bone marrow transplantation

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Abstract

Echocardiography was performed in 16 children undergoing bone marrow transplantation (BMT) for mucopolysaccharidoses. Cardiac involvement before BMT was detected in seven (44%). One year after BMT (11 patients/five with cardiac involvement), left ventricular restriction resolved in 2/3 patients and hypertrophy in one. In the remainder, at mean follow up of 2·5 years, no progression of pre-existing or development of new cardiac involvement was noted. It is concluded that in a significant proportion of patients with mucopolysaccharidoses, cardiac involvement improved after BMT.

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Bone marrow transplantation (BMT) has been employed for children with mucopolysaccharidoses.[1 2] Left sided cardiac abnormalities, in the form of mitral and/or aortic valve dysplasia and primary myocardial involvement (cardiomyopathy) are well documented in these children.[3 4] It is unknown whether these cardiac abnormalities change after BMT. The purpose of this study was to assess any changes in the cardiac status of patients undergoing BMT for one of the mucopolysaccharidoses.

Patients and methods

We studied a total of 16 children (age range 3–108 months, median 14·5 months) with a mucopolysaccharidosis (table), who were entering the BMT programme at Westminster Children's Hospital between 1988 and 1993. The indications for BMT varied according to the diagnosis of mucopolysaccharidosis (MPS I, MPS IV, MPS VI). Bone marrow from a suitable donor was used, after a standard induction regimen of busulphan and cyclophosphamide. Cardiac status was evaluated clinically and echocardiographically before BMT, 6–12 months after, and at yearly intervals thereafter. Patients were studied with clinical examination, two dimensional, M mode, continuous, and pulsed wave Doppler echocardiography, and colour Doppler mapping. Sequential, analysable data were available in these 16 patients, who do not account for the total number of patients with a mucopolysaccharidosis who underwent BMT during this period. Diastolic ventricular function was assessed from the transmitral/transtricuspid Doppler filling characteristics. Restrictive cardiomyopathy, characteristically seen in myocardial storage disease such as amyloid was defined as a short (<150 ms) mitral or tricuspid deceleration time and a ratio of early to late diastolic transmitral flow velocity >2.[5]

Details of patients studied

Patient No (sex)	*Diagnosis*	*Age at BMT (months)*	*Echocardiography*	
			Before BMT	*After BMT*
1 (M)	MPS1	3 Awaiting	AS/MV dysplasia	
2 (F)	MPS1	6, 18	Restrictive LV/LV+	6/12 Resolved*
3 (M)	MPS1	7	Restrictive LV	12/12 Resolved
4 (F)	MPS1	Died before BMT	Normal	
5 (M)	MPS1	10	Normal	Normal
6 (M)	MPS1	12 Awaiting	Normal	
7 (F)	MPS1	12	Normal	No follow up echocardiography
8 (M)	MPS1	13	Normal	Normal
9 (M)	MPS1	16 Rejected (developmental delay)	Normal	Normal
10 (M)	MPS1	18	Normal	Normal
11 (F)	MPS1	20	Normal	Normal
12 (F)	MPS1	24	Normal	Normal
13 (F)	MPS1	54 Off BMT list	MV dysplasia, restrictive LV	
14 (M)	MPS4	63	AS/LVH+	No change
15 (M)	MPS6	104	Restrictive LV	No change
16 (F)	MPS6	108	MV dysplasia, LVH+	LVH+ resolved

MPS1: Hurler's disease, MPS4: Morquio's syndrome, MPS6: Maroteaux-Lamy syndrome. AS: aortic stenosis, MV: mitral valve, LV: left ventricle, LV+: left ventricular dilatation, LVH: left ventricular hypertrophy. *After second (successful) BMT.

Results

We detected cardiac involvement before BMT in seven (44%) patients (table). Left heart structural involvement, in the form of mitral or/and aortic dysplasia, was encountered in four. Two of them had mild-moderate concentric left ventricular hypertrophy, the magnitude of which was disproportionate to their valvular abnormalities. Relative thickness of the posterior wall compared with left ventricular dimension at end diastole (LVW/LVEDD) was significantly higher in these two patients (mean 0·22) compared with the remainder ($p<0·005$). There was mild mitral regurgitation on colour Doppler mapping in two, without significant stenosis. One of the two patients with aortic valve dysplasia had mild stenosis (Doppler gradient 25 mm Hg). Systolic ventricular function was normal (shortening fraction 29–37%) in all. Four patients had a restrictive Doppler left ventricular inflow pattern (one with mild left ventricular dilatation) with a short E wave deceleration time (mean 117·5 ms) and absent or minimal transmitral flow during atrial systole. None of the patients with cardiac abnormalities was haemodynamically compromised at the time of the study. Eleven of the 16 patients (table) underwent successful BMT during the study period (one patient required a second BMT 12 months later having rejected the first graft).

Two patients were taken off the transplant list because of severe developmental delay (after graft rejection in one). One patient died from non-cardiac causes, while waiting for a transplant, and two patients were awaiting suitable donors. At the first follow up after BMT (6–12 months) all 11 patients were alive and well. Echocardiography showed neither changes in pre-existing valvar dysplasias nor development of any new cardiac lesions. The restrictive left ventricular physiology resolved in two out of three patients, with normalisation of the pulsed wave Doppler transmitral flow (E wave deceleration time >150 ms and E/A wave peak velocities 1·2 and 1·4 respectively). There was another patient (16) with mild-moderate concentric left ventricular hypertrophy (LVW/LVEDD=0·23) and mitral valve dysplasia before transplant in whom there was resolution of hypertrophy (LVW/LVEDD=0·16). During further follow up ranging from 6 months to 4·5 years (mean 2·5 years) there was no further progression or development of new cardiac lesions. No effects of BMT on left ventricular function were seen in patients with cardiac sparing before BMT.

Discussion

Our study shows a high prevalence of left sided cardiac involvement in children with a mucopolysaccharidosis, in keeping with previous reports. Structural lesions were more common in older patients, but diastolic dysfunction was seen across the age range. Primary myocardial involvement and infiltration of coronary arteries with mucopolysaccharides are recognised complications and may lead to impaired ventricular function. Sudden death in these patients has been assumed to be due to arrhythmias. Although the number of patients studied was small, some tentative conclusions can be drawn. In 60% of our successfully transplanted patients cardiac involvement appeared to improve within the first year of follow up. This improvement was confined to previous left ventricular dysfunction and hypertrophy and not of structural abnormalities of the valves; it was seen mainly in younger patients. Furthermore there was no progression of pre-existing or development of new cardiac lesions in our transplanted patients. These findings, we would speculate, may be due to clearing of mucopolysaccharide deposition in the heart.[6] Successful BMT makes it possible for blood cells and derived macrophages to be replaced by genetically normal cells with the ability to produce and transfer the defective enzyme. This in turn may lead to clinical improvement of various systems (and organs) including the heart. There was a trend towards improved cardiac outcome among our younger transplanted patients. This could mean that some of the cardiac changes, seen in the mucopolysaccharidoses, become irreversible after a certain age.

Our data suggest that BMT for a severe mucopolysaccharidosis has some beneficial medium term cardiac effects mainly in younger patients. This could be an additional consideration in favour of early BMT, when clinically indicated.

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