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# Natural history of echocardiographic abnormalities in mucopolysaccharidosis III

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ABSTRACT

*Background:* Mucopolysaccharidosis (MPS) type III, Sanfilippo Syndrome, is an autosomal recessive lysosomal storage disorder. MPS I and II patients often develop cardiac involvement leading to early mortality, however there are limited data in MPS III. The objective of this study is to describe cardiac abnormalities in a large group of MPS III patients followed in a longitudinal natural history study designed to determine outcome measures for gene transfer trials.

*Methods:* A single center study of MPS III patients who were enrolled in the Nationwide Children's Hospital natural history study in 2014. Two cardiologists reviewed all patient echocardiograms for anatomic, valvular, and functional abnormalities. Valve abnormalities were defined as abnormal morphology, trivial mitral regurgitation (MR) with abnormal morphology or at least mild MR, and any aortic regurgitation (AR). Abnormal left ventricular (LV) function was defined as ejection fraction $< 50\%$. Group comparisons were assessed using two-sample *t*-tests or Wilcoxon rank sum tests for continuous variables and chi-square or Fisher's exact tests for categorical variables.

*Results:* Twenty-five patients, 15 Type A and 10 Type B MPS III, underwent 45 echocardiograms. Fifteen patients (60%) demonstrated an abnormal echocardiographic finding with age at first abnormal echocardiogram within the study being $6.8 \pm 2.8$ years. Left-sided valve abnormalities were common over time: 7 mitral valve thickening, 2 mitral valve prolapse, 16 MR (8 mild, 8 trivial), 3 aortic valve thickening, and 9 AR (7 mild, 2 trivial). Two patients had asymmetric LV septal hypertrophy. No valvular stenosis or ventricular function abnormalities were noted. Incidental findings included: mild aortic root dilation (2), bicommissural aortic valve (1), and mild tricuspid regurgitation (3).

*Conclusions:* Individuals with Sanfilippo A and B demonstrate a natural history of cardiac involvement with valvular abnormalities most common. In short-term follow up, patients demonstrated only mild progression of abnormalities, none requiring intervention. Valvular disease prevalence is similar to MPS I and II, but appears less severe. These findings raise no specific concerns for gene transfer trials in patients in this age range.

## 1. Introduction

Mucopolysaccharidosis (MPS) type III, Sanfilippo Syndrome, is an autosomal recessive lysosomal storage disorder with four described subtypes typically diagnosed in early childhood [1]. Patients with MPS disorders lack one of many enzymes necessary for glycosaminoglycan (GAG) breakdown, and as a result have an accumulation of GAGs in various tissues within the body [2]. The proposed mechanism for cardiac involvement in MPS is accumulation of GAGs within the cardiac valves, coronary arties, great vessels, and cardiac myocytes [3,4]. MPS I and II patients often develop cardiac involvement leading to early mortality, with reports of adult MPS patients who have been treated or have attenuated disease phenotypes surviving to require cardiac valve replacement, coronary artery disease interventions, and treatment for heart block and heart failure [5]. Cardiac involvement described in children with MPS I and II – two MPS disorders with the most clinical

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similarities to MPS III – includes abnormal valve morphology resultant in valve dysfunction, ventricular dysfunction, and asymmetrical left ventricular hypertrophy [6–8].

There are limited data on cardiac involvement in patients with MPS III [9]. Unlike several other MPS disorders, there is no available enzyme replacement therapy nor has there been a satisfactory response to hematopoietic stem cell transplant as seen in MPS I. With new treatments such as viral gene transfer and enzyme replacement therapies being evaluated in clinical trials, it is important to define the prevalence of cardiac involvement in this patient population, in order to differentiate this from any cardiac complications arising from experimental therapies as well as to anticipate future health care needs should one of these therapies prove successful in improving life expectancy. The objective of this study is to describe cardiac abnormalities in a large group of MPS III patients followed in a longitudinal natural history study designed to determine outcome measures for gene transfer trials.

## 2. Materials and methods

This study is a single center study of MPS III patients who were enrolled in the Nationwide Children's Hospital natural history study which enrolled patients in 2014 with a year-long follow up [10]. Two cardiologists reviewed all patient echocardiograms performed at Nationwide Children's Hospital during the course of the study for anatomic, valvular, and functional abnormalities. Four patients had studies performed at outside facilities. Direct image visualization was performed for one of these patients. For the other three patients, data was obtained from finalized echocardiogram reports. Valve abnormalities were defined as abnormal valve morphology, trivial mitral regurgitation (MR) with abnormal morphology or at least mild MR, or any amount of aortic regurgitation (AR). Valvular regurgitation was graded using the guidelines and standards reported by the American Society of Echocardiography (ASE) [11]. Abnormally decreased left ventricular (LV) function was defined as ejection fraction < 50% by Simpson's method. Ventricular dimensions were evaluated by 2 dimensional M-mode measurements for hypertrophy or dilation as per ASE guidelines [12]. Group comparisons were assessed using two-sample *t*-tests or Wilcoxon rank sum tests for continuous variables and chi-square or Fisher's exact tests for categorical variables.

## 3. Results

Twenty-five MPS III patients, 15 Type A and 10 Type B, underwent 45 echocardiograms as a part of the Nationwide Children's Hospital natural history study. Fifteen patients (60%) demonstrated an abnormal echocardiographic finding during the study, with age at first abnormal echocardiogram within the study being 6.8 ± 2.8 years.

At the time of first echocardiogram, patients displayed evidence of cardiac abnormalities (Table A.1) including 6 patients with abnormal mitral valve morphology and 12 with mitral valve regurgitation; 5 patients with abnormal aortic valve morphology and 8 aortic valve regurgitation; and 2 patients displayed left ventricular hypertrophy. There was a trend towards older patients having a higher degree of mitral regurgitation at the first echocardiogram ($p = .0551$). No age difference was noted with other echocardiographic abnormalities. Patients with MPS III subtype B had a higher incidence of mitral valve regurgitation at time of first echocardiogram ($p = .016$) (Table A.2), although the cohort of patients with subtype B were, on average, older than those with subtype A (8.7 years at enrollment versus 4.96). There were no other differences noted with other echocardiographic abnormalities between subtypes.

During the course of the study, abnormalities detected in this patient population included aortic and mitral valve abnormalities, aortic and mitral valve regurgitation, and asymmetric left ventricular hypertrophy with no difference noted between subtypes A and B over time (Table A.3). Left-sided valve abnormalities were most common over time (Fig. A.1): 7 mitral valve thickening, 2 mitral valve prolapse, 16 mitral regurgitation (8 mild, 8 trivial), 3 aortic valve thickening, and 9 aortic regurgitation (7 mild, 2 trivial). Two patients had asymmetric LV septal hypertrophy. No patients demonstrated evidence of valvular stenosis or ventricular dysfunction during the course of the study. Incidental findings included two patients with mild aortic root dilation, one patient with bicommissural aortic valve, and three patients with mild tricuspid regurgitation. Of the 9 patients who demonstrated significant valve findings during the course of the study, only 3 were noted to have an abnormality on cardiac auscultation by the investigators (a neuromuscular physician and two clinical geneticists) in the form of a Grade I to II systolic ejection murmur.

## 4. Discussion

Children with Sanfilippo A and B in this study demonstrate a natural history of cardiac involvement, with valvular abnormalities most common. This is similar to findings reported in studies with a smaller number of patients with MPS III [2–4,6,7,9,13–15]. Mitral and aortic valve abnormalities were more common than tricuspid or pulmonary valve involvement. Mitral valve disease was more prevalent in the older children in the study, but no correlation with age was seen among the other abnormalities. Overall, valvular disease prevalence is similar to MPS I and II, but appears less severe [5,8]. Two patients in our study also demonstrated aortic root dilation which may be an incidental finding, however this has also been previously reported in the literature [15]. In short-term follow up, patients demonstrated only mild progression of abnormalities, none requiring intervention.

These findings raise no specific safety concerns for viral gene transfer and other therapeutic trials in patients in this age range. This study was limited to children with the more typical severe childhood presentation of MPS IIIA and IIIB, but who were not in the end stages of disease. Future areas of needed study include larger cohorts of patients with attenuated forms of MPS III, including adults, comprising a significant minority of affected patients in many populations throughout the world. Additionally, this study did not include electrocardiography, in which abnormalities such as heart block have been described in patients with MPS II and VI and even in adults with MPS III [5].

Enzyme replacement therapies for other MPS disorders have not reversed already established valvular disease, though may stabilize it [14]. It remains to be seen whether a successful viral gene transfer therapy would result in a similar cardiac outcome. Viral serotype and tropism may have an influence in mediating any direct effects in excess of those mediated by uptake of circulating enzyme.

Physical findings early in the course of MPS III can be subtle, and the discovery of a thickened or leaking left-sided cardiac valve can be one more clue to add to others that might be present at that time, such as: hirsutism, hepatomegaly, coarsening of the hair and facial features, recurrent otitis media, and hearing loss. Early recognition of the physical findings of MPS III will be all the more critical should an effective therapy be found; without their recognition, these children often go undiagnosed for the period of time during which their only obvious symptoms are developmental delay and behavioral issues. As a neurodegenerative lysosomal storage disorder, earlier therapy may be expected to have a better outcome.

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