



Natural history of cardiac findings in mucopolysaccharidosis type I: report from an international registry

Original Article

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Abstract

Mucopolysaccharidosis type I is an inborn error of glycosaminoglycan catabolism with phenotypes ranging from severe (Hurler syndrome) to attenuated (Hurler–Scheie and Scheie syndromes). Cardiovascular involvement is common and contributes significantly to morbidity and mortality. We conducted a retrospective analysis of the prevalence and natural history of cardiac abnormalities in treatment-naïve individuals enrolled in the international Mucopolysaccharidosis Type I Registry. Interrogation of echocardiography data (presence of cardiac valve regurgitation and/or stenosis; measurements of left ventricular chamber dimensions in diastole and systole, diastolic left ventricular posterior wall and interventricular septal thicknesses and ventricular systolic function (shortening fraction)) showed that mitral regurgitation was the most common and earliest finding for individuals with both severe (58.3%, median age 1.2 years) and attenuated (74.2%, median age 8.0 years) disease. Left-sided valve stenosis was also common in individuals with attenuated disease (mitral 30.3%; aortic 25%). Abnormal ventricular wall and septal thickness (Z-scores ≥ 2) were observed early in both phenotypes. Z-scores for diastolic left ventricular posterior wall and interventricular septal thicknesses increased with age in the severe phenotype (annualised slopes of 0.2777 [$p = 0.037$] and 0.3831 [$p = 0.001$], respectively); a similar correlation was not observed in the attenuated phenotype (annualised slopes of -0.0401 [$p = 0.069$] and -0.0029 [$p = 0.875$], respectively). Decreased cardiac ventricular systolic function (defined as shortening fraction $<28\%$) was uncommon but, when noted, was more frequent in infants with the severe phenotype. While cardiac abnormalities occur early in both severe and attenuated mucopolysaccharidosis type I, the pattern of valve dysfunction and progression of ventricular abnormalities vary by phenotype.

Introduction

Mucopolysaccharidosis type I is an autosomal recessive lysosomal storage disease resulting from a deficiency of α -L-iduronidase, a lysosomal enzyme responsible for metabolism of the glycosaminoglycans dermatan and heparan sulfate.¹ Occurring in 1/100,000 live births,² mucopolysaccharidosis type I has a range of disease phenotypes from severe (Hurler syndrome, which always has central nervous system involvement) to attenuated (Hurler–Scheie and Scheie syndromes).¹ Glycosaminoglycan accumulation results in a broad range of visceral involvement, including hepatosplenomegaly, skeletal and joint deformity (i.e., dysostosis multiplex), respiratory issues (e.g., obstructive sleep apnoea and infections), and progressive cardiac disease.^{3,4}

Treatment options include hematopoietic stem cell transplant (recommended before 2 years of age) for individuals with severe mucopolysaccharidosis type I, and enzyme replacement therapy with laronidase (recombinant human α -L-iduronidase; Aldurazyme[®]) for the treatment of individuals with non-central nervous system manifestations, since laronidase does not cross the blood–brain barrier.^{4–7} In the absence of treatment, life expectancy is limited to the first decade of life for those with severe disease, while premature death due to respiratory and cardiac disease is common in the attenuated phenotype.² The diagnosis of mucopolysaccharidosis type I requires evidence for glycosaminoglycan storage and decreased functional activity of the corresponding enzyme and/or mutation analysis.^{8,9}

Regardless of disease severity, somatic findings in most individuals with mucopolysaccharidosis type I include cardiac pathology, including valvulopathy, ventricular hypertrophy, myointimal proliferation of epicardial coronary arteries, and aortic root dilation, while rhythm

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disturbances remain infrequent.^{10–12} Since cardiac valvulopathy has not been reversed with current therapies, it has become a frequently studied benchmark of treatment efficacy.^{13–16} Cardiac ultrasound has been the primary clinical modality used in cardiac studies of mucopolysaccharidosis type I. Colour flow Doppler, which has greatly increased the ability to detect cardiac valve disease, was first reported in a study of mucopolysaccharidoses in 1995.¹⁷

With the availability of hematopoietic cell transplantation and enzyme replacement therapy, obtaining the natural history of untreated mucopolysaccharidosis type I has become exceedingly difficult. Cardiac valve disease, ventricular hypertrophy, and cardiomyopathy have been previously described as disease components in untreated individuals; however, studies have involved small numbers, often from a single institution or as part of a collective study of all mucopolysaccharidoses.^{17–31} Cardiac valve dysfunction, particularly involving left-sided valves, has been reported both in the very youngest children with severe disease^{10,32,33} as well as adults with attenuated disease.^{10,23,29,30,34,35} However, some studies report only valve “dysfunction” without further defining whether it is valve regurgitation or stenosis.¹⁸ Natural history studies similarly report small numbers of patients, with most studies describing the cardiac response after either hematopoietic cell transplantation or enzyme replacement therapy.^{13–15,20,22,24,36–41}

The Mucopolysaccharidosis Type I Registry is a voluntary, observational, and global database established in 2003 to characterise the natural history of mucopolysaccharidosis type I and to evaluate clinical outcomes after enzyme replacement therapy with the ultimate goal of creating evidence-based guidelines for patient management.¹⁰ A previous report from the international Mucopolysaccharidosis Type I Registry tallying systemic complications in almost 1000 individuals reported that nearly half of those with severe disease and two-thirds with the most attenuated form had cardiac valve abnormalities,³ but the abnormalities were not further defined. Therefore, we analysed the prevalence and natural history of cardiac abnormalities in treatment-naïve individuals with mucopolysaccharidosis type I enrolled in the international Mucopolysaccharidosis Type I Registry.

Materials and methods

Mucopolysaccharidosis Type I Registry

The Mucopolysaccharidosis Type I Registry (<https://clinicaltrials.gov>, NCT00144794) is supported and maintained by Sanofi (Cambridge, MA) and is overseen and directed by an independent Board of Advisors comprised of physicians who are experts in the care of people living with mucopolysaccharidosis.

All registrants have confirmation of mucopolysaccharidosis type I diagnosis by either mutation analysis or measurement of leucocyte alpha-L-iduronidase levels. Informed consent is required of all participants before enrolment in the registry. As of December 2012, each participating site has been required to have approval from an institutional review board or ethics committee for registry participation³. Participating sites complete enrolment forms that include demographics, a multi-domain medical history related to the presence and onset of symptoms, and the type and starting date of any treatment for each participant. Clinical event forms are periodically completed for follow-up of specific aspects of disease progression.

Study population

Treatment naïve registrants with at least one echocardiography assessment prior to either hematopoietic stem cell transplant or the initiation of enzyme replacement therapy and with physician-reported phenotype were included. Data entered in the registry as of February 2017 were included. Individuals reported as having severe disease who were diagnosed at greater than 12 years old or who were 12 years or older at any echocardiographic assessment were excluded due to likely misclassification of phenotype.

Echocardiography assessments

Information on the results of echocardiography assessments is collected on a cardiovascular and respiratory clinical event form, including the presence of cardiac valve regurgitation and/or stenosis for each of the four cardiac valves (aortic, mitral, pulmonary, and tricuspid valves). Valve regurgitation and stenosis are not further quantified. Standard measurements of left ventricular chamber dimensions (in diastole and systole), and left ventricular posterior wall and interventricular septal thicknesses (the latter in diastole) are recorded. Left ventricular function, assessed by shortening fraction (a measure of the change in linear dimensions between diastole and systole expressed as a percentage of the diastolic dimension), is also recorded. A usable response was defined for all parameters as one with a yes/no or numeric response; “unknown” and “not assessed” responses were not used.

Performance and timing of voluntary echocardiography assessments were determined by treating physicians. All available echocardiography assessments completed prior to treatment initiation were used. Not all individuals had complete data in each echocardiogram report, and the number and timing of echocardiography assessments varied across participants.

Analysis subgroups

All participants with at least one echocardiogram during the natural history period with a response to at least one valve function item were included in the analyses of the prevalence and age at the first report of valvular dysfunction. Subgroups for additional analyses are shown in Supplemental Figure 1. Descriptive analyses of chamber dimensions and shortening fractions were conducted for those with both valve dysfunction data and at least one echocardiogram report of ventricular dimensions and/or shortening fraction. The mixed model analyses of changes in ventricular dimension and function over time (described below) were conducted for the subset of participants with at least two measures of cardiac dimension or function over time.

Statistical analyses

All analyses were stratified by disease phenotype (i.e., severe or attenuated). Demographic characteristics were presented as counts and percentages or as means, standard deviations, medians, and 25th to 75th percentiles, as appropriate. The presence of stenosis and/or regurgitation for aortic, mitral, pulmonary, and tricuspid valves and the corresponding ages at first reported valve dysfunction were compared between the severe and attenuated phenotypes using chi-square or (non-parametric) Wilcoxon rank-sum tests.

Left posterior wall thicknesses, interventricular wall thickness, and chamber dimensions were converted to Z-scores based on body surface area using the DuBois formula.⁴² Height and weight for Z-score calculation were obtained from clinical evaluation

forms within ± 6 months of each echocardiograph report. The presence of any Z-score greater than 2 was considered abnormal. Raw values for shortening fraction as a measure of left ventricular function were collected, and values $<28\%$ were considered abnormal.

Linear mixed effect models were used to estimate changes over time for the ventricular dimension measurements and shortening fraction. These models account for repeated measures within individuals over time. An unstructured covariance matrix was used, and models were estimated using restricted maximum likelihood. The timescale was the age at each echocardiograph measurement. The final models included a random intercept and fixed effects for age, phenotype (attenuated or severe), and an interaction term between age and phenotype (i.e., age x phenotype) to allow different rates of change among those with attenuated and severe disease. An estimated slope (i.e., annual change in ventricular dimension/shortening fraction) was determined for the severe and attenuated populations. The associated p value indicated whether each slope was statistically different from zero. The p value for the interaction between phenotype and age was used to determine whether the slopes for the severe versus attenuated populations were significantly different from each other. All statistical analyses were two-sided and carried out using SAS v. 9.3 (SAS Institute, Cary, NC).

Results

Participant and echocardiography data

There were 1010 individuals enrolled in the registry as of February 2017, 659 (65.2%) with severe disease and 351 (34.8%) with attenuated disease (Supplemental Figure 1). Among these registrants, 761 had data from at least one echocardiogram during the natural history period, 496 with severe disease, and 265 with attenuated disease. Demographic characteristics for this cohort are shown in Table 1. The proportion of males and females was similar in both groups. The mean ages at diagnosis and first echocardiogram were younger in the severe group compared to the attenuated group. Those with severe disease had less natural history follow-up time, with a median of 1.4 years versus 10.3 years for the attenuated group. The majority of individuals with echocardiograms were from Europe/Middle East/Africa ($n = 369$, 48.5%) or North America ($n = 323$, 42.4%), and the remainder were from South America ($n = 62$, 8.1 %) or Asia ($n = 7$, 0.9 %).

Among 761 participants, there were 4444 echocardiography reports, 3119 (70.2%) among the severe group and 1325 (30%) among the attenuated group. The median number of reports per individual was greater for the severe group (5, range 1–42) than for the attenuated group (3, range 1–36). Most reports were from 1990 or later ($n = 4306/4444$, 97%).

Valve dysfunction

Among 760 individuals with at least one response to the valve dysfunction question, 160 (21.1%) never reported valve dysfunction ($n = 128/496$, 25.8% with severe disease and $n = 32/264$, 12.1% with attenuated disease). Among the 600 individuals who ever reported valve dysfunction, most had a “yes” response at their first valve function assessment ($n = 319/368$, 86.7%, severe and $n = 199/232$, 85.8%, attenuated). Median (25th, 75th percentile) ages at the first report of valve dysfunction were 1.2 (0.8, 2.1) and 7.5 (4.5, 14.9) years for the severe and attenuated groups, respectively. When “no” was the response to the presence of valve

Table 1. Characteristics of MPS I Registry participants with at least one echocardiogram during the natural history period

	Participants	
	Severe MPS I n = 496	Attenuated MPS I n = 265
Female, n (%)	247 (49.8)	147 (55.5)
Male, n (%)	249 (50.2)	118 (44.5)
Age at MPS I diagnosis		
Mean (SD)	1.1 (1.0)	7.4 (8.8)
Median (IQR)	0.9 (0.6, 1.3)	4.7 (3.1, 8.4)
Age at the time of first echocardiogram		
Mean (SD)	1.6 (1.7)	10.6 (10.4)
Median (IQR)	1.2 (0.7, 1.8)	6.7 (3.8, 13.6)
First echocardiogram before MPS I diagnosis, n (%)	115 (23.2)	54 (20.4)
Individuals with any “yes” valve dysfunction response, n (%)	368 (74.2)	232 (87.6)
“Yes” on first response, n (%)	319 (64.3)	199 (75.1)
Age at “yes” on first response		
Mean (SD)	1.8 (1.8)	11.8 (11.1)
Median (IQR)	1.2 (0.8, 2.1)	7.5 (4.5, 14.9)
Individuals with any “no” valve dysfunction response, n (%)	128 (25.8)	32 (12.1)
“No” on first response, n (%)	177	65
Age at “no” on first response		
Mean (SD)	1.3 (1.3)	6.9 (6.8)
Median (IQR)	1.0 (0.6, 1.6)	4.9 (2, 10)
Natural history follow-up time*		
Mean (SD)	2.5 (2.6)	13.7 (11.3)
Median (IQR)	1.4 (1.0, 2.6)	10.3 (5.4, 18.4)

IQR = interquartile range; MPS I = mucopolysaccharidosis type I; SD standard deviation.

*Natural history follow-up time was calculated from birth to last known follow-up date for treatment-naïve individuals. For individuals who received enzyme replacement therapy or had hematopoietic stem cell transplant, natural history follow-up time was calculated from birth to date of first treatment. Echocardiograph report included LVPWd, IVSd, LVed, LVes, and shortening fraction.

dysfunction, median (25th, 75th percentile) ages were younger: 1.0 (0.6, 1.6) and 4.9 (2, 10) for the severe and attenuated groups, respectively. Natural history follow-up was 1.4 (1.0, 2.6) and 10.3 (5.4, 18.4) years for the severe and attenuated groups, respectively.

Specific valve dysfunction by disease phenotype is shown in Table 2. Percent of individuals with valve dysfunction is shown in Figure 1A (stenosis) and 1B (regurgitation). Apart from tricuspid regurgitation, which occurred in greater than 30% of individuals, left-sided valve disease was more common than right-sided valve disease in both the severe and attenuated groups. By contrast, right-sided valve findings (apart from tricuspid regurgitation) occurred in less than 15% of participants and were not significantly different between the severe and attenuated phenotypes.

Age at presentation of valve dysfunction was significantly higher in individuals with attenuated disease compared to severe

Table 2. Echocardiographic description of valve dysfunction among individuals with severe or attenuated MPS I during the natural history period

Valve dysfunction	Severe MPS I n = 496	Attenuated MPS I n = 264	p-Value*
Left side			
Aortic stenosis, n (%)	18 (3.6)	66 (25.0)	<0.0001
Age, first reported, years			
Mean (SD)	2.9 (2.9)	18.2 (10.3)	<0.0001
Median (IQR)	1.6 (1.0, 5.0)	17.0 (9.5, 25.0)	
Aortic regurgitation/insufficiency, n (%)	101 (20.4)	87 (33.0)	0.0001
Age, first reported, years			
Mean (SD)	2.1 (2.2)	17.0 (12.7)	<0.0001
Median (IQR)	1.4 (0.9, 2.1)	13.0 (7.8, 23.3)	
Mitral stenosis, n (%)	45 (9.1)	80 (30.3)	<0.0001
Age, first reported, years			
Mean (SD)	3.5 (2.7)	15.2 (11.0)	<0.0001
Median (IQR)	3.0 (1.2, 5.0)	12.2 (7.1, 19.0)	
Mitral regurgitation/insufficiency	289 (58.3)	196 (74.2)	<0.0001
Age, first reported, years			
Mean (SD)	1.8 (1.81)	11.8 (10.78)	<0.0001
Median (IQR)	1.2 (0.9, 2.0)	8.0 (4.7, 15.5)	
Mitral Prolapse	83 (16.7)	40 (15.2)	0.5728
Age, first reported, years			
Mean (SD)	2.1 (1.9)	6.5 (5.4)	<0.0001
Median (IQR)	1.6 (1.0, 2.2)	4.6 (3.3, 8.0)	
Right side			
Tricuspid stenosis, n (%)	7 (1.4)	6 (2.3)	0.3832
Age, first reported, years			
Mean (SD)	2.5 (1.2)	15.1 (18.2)	0.0034
Median (IQR)	2.7 (1.1, 3.2)	12.5 (9.8, 17.1)	
Tricuspid regurgitation/insufficiency, n (%)	194 (39.1)	81 (30.7)	0.0213
Age, first reported, years			
Mean (SD)	1.9 (2.0)	14.3 (12.4)	<0.0001
Median (IQR)	1.2 (0.8, 2.0)	10.2 (6.2, 17.0)	
Pulmonary stenosis, n (%)	18 (3.6)	11 (4.2)	0.7126
Age, first reported, years			
Mean (SD)	2.9 (2.8)	15.4 (13.8)	0.0008
Median (IQR)	2.3 (1.0, 3.8)	7.9 (5.8, 30.3)	
Pulmonary regurgitation/insufficiency, n (%)	60 (12.1)	28 (10.6)	0.5408
Age, first reported, years			
Mean (SD)	1.7 (1.5)	12.6 (10.6)	<0.0001
Median (IQR)	1.3 (0.8, 1.9)	10.4 (4.7, 15.0)	

disease (Table 2, Fig. 1C-D). Mitral regurgitation was the most common and earliest finding for individuals with both severe (58.3%, median age 1.2 years) and attenuated (74.2%, median age 8.0 years) disease. Mitral regurgitation occurred twofold more

frequently than the next most common finding, aortic regurgitation, in both the severe (20.4%) and attenuated (33.0%) phenotypes.

The most notable difference in valve dysfunction between severe and attenuated phenotypes was the development of mitral

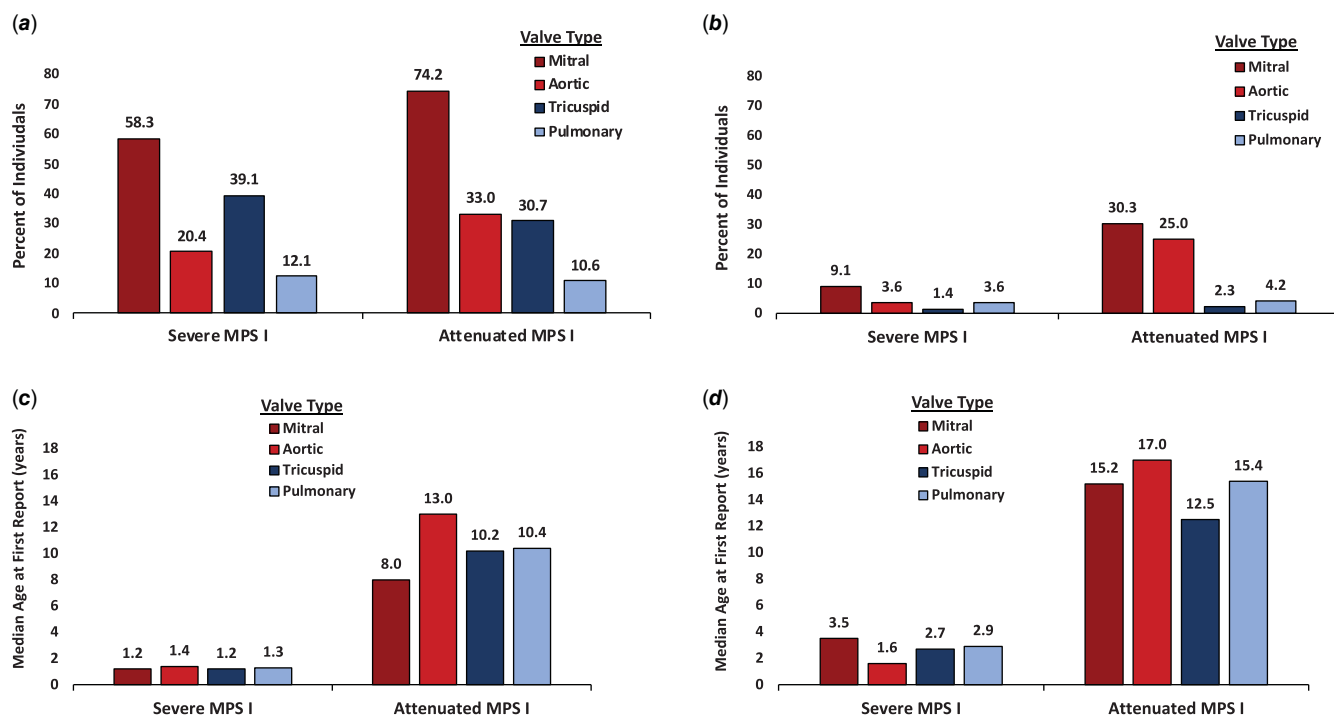


Figure 1. Valve dysfunction and ventricular dimension and function in severe and attenuated MPS I. A. Percent of individuals with valve regurgitation. B. Percent of individuals with valve stenosis. C. Median age (years) of first report of valve regurgitation. D. Median age of the first report of valve stenosis. E. Percent of individuals with abnormal (Z-scores ≥ 2) for left ventricular posterior wall (LVPWd) or intraventricular septal (IVSd) thicknesses in diastole by age group. F. Percent of individuals with abnormal (Z-scores ≥ 2) for left ventricular end-diastolic (LVed) and end-systolic (LVes) dimensions by age group. G. Percent of individuals with decreased shortening fraction ($<28\%$) by age group. For data in panels A–D: The denominator used for each group is the total number of individuals with any (yes or no) valve dysfunction data. For data in panels E–G: An individual may have had reports from multiple exams at different ages. Numbers in the table below the bar graphs are the numbers of individuals with abnormal results over the number of individuals with available data.

and aortic stenosis in individuals with attenuated disease. Mitral stenosis occurred in only 9.1% of severely affected individuals, compared to 30.3% of those with attenuated disease. Similarly, aortic stenosis occurred in only 3.6% of individuals with the severe phenotype but in 25.0% of those with attenuated disease. Except for mitral prolapse, left-sided valve abnormalities were significantly more frequent in individuals with the attenuated phenotype ($p \leq 0.0001$ for each type).

Ventricular dimension and function

Table 2 includes ventricular dimension and function data overall and with data restricted to assessments done prior to or at the time of diagnosis. Prevalence of increased (i.e., Z-scores ≥ 2) posterior wall and septal thickness and ventricular chamber dimensions and decreased shortening fraction (i.e., $<28\%$) was higher in those with severe versus attenuated disease. Left ventricular hypertrophy of the posterior wall was the most common finding in both phenotypes (47.7 and 31% in severe and attenuated, respectively). Increased left ventricular chamber dimensions in diastole and systole and septal thickness were reported in approximately 1/3 of individuals with severe disease compared to 8–16% of those with the attenuated phenotype (Table 2). Among the small proportion ($<20\%$) of individuals with dimension data available before or at the time of diagnosis, 24–37% of those with severe disease and 9–20% of those with attenuated disease had abnormal cardiac dimension results.

Figure 1E and F show the distribution of abnormal ventricular dimensions and function by age groups for each phenotype.

Abnormalities in ventricular wall and septal thickness were observed early and generally occurred with similar frequency across age groups in the severe phenotype, although there were few individuals older than 5 years of age for comparison (Fig. 1E). Abnormal diastolic and systolic dimension Z-scores occurred with the greatest frequency in individuals less than 6 months of age (Fig. 1F). Among individuals with attenuated disease, chamber wall thickness and dimension abnormalities were most frequent in those less than 5 years and greater than 20 years of age (Fig. 1E and F).

Decreased cardiac systolic function (shortening fractions $<28\%$) occurred in less than 20% of individuals with either phenotype (16.1% and 6.7% with severe and attenuated phenotypes, respectively) (Table 3) and occurred with the greatest frequency (27.3%, $n = 12/44$) among individuals with severe disease who were 6 months of age or younger (Fig. 1G).

Mixed model analysis was used to assess changes in Z-scores over time. Figure 2A and B show estimated changes in Z-scores over time for left ventricular posterior wall thickness and interventricular septal thickness, respectively. Left ventricular posterior wall Z-scores increased significantly with time in the severe phenotype (estimated slope 0.2777 units/year, p value = 0.037) while remaining stable in the attenuated phenotype (estimated slope -0.0401 units/year, $p = 0.069$). The difference between slopes in the two groups was statistically significant ($p = 0.019$). Results were similar for interventricular septal thickness (estimated slopes 0.3831 and -0.0029 units/year for the severe and attenuated phenotypes, respectively, p -value for difference by phenotype = 0.001).

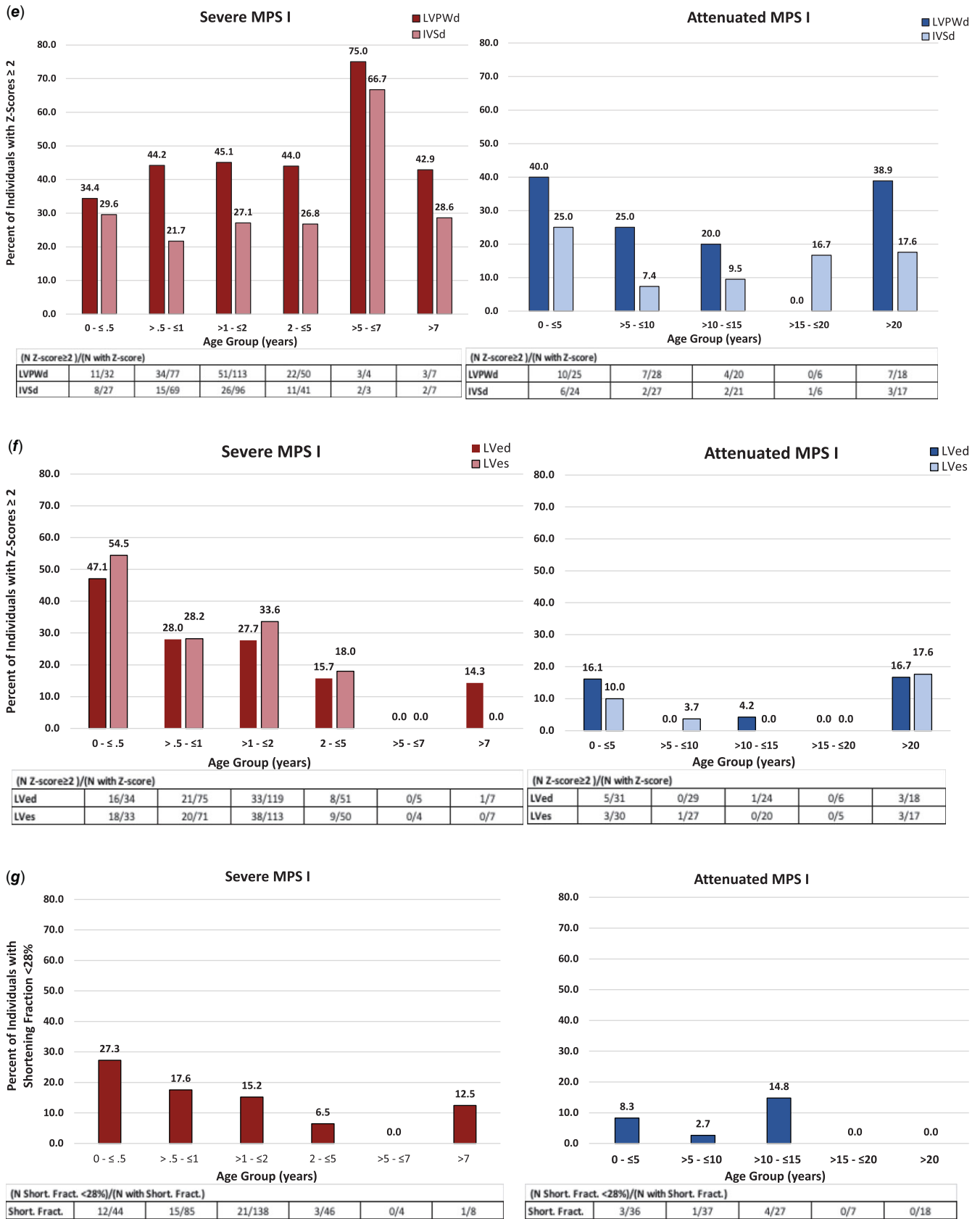


Figure 1. (Continued).

Table 3. Echocardiographic description of ventricular dimensions and function during the natural history period

Ventricular dimension and function	Severe MPS I	Attenuated MPS I	Total
LVPWd			
	n = 237	n = 87	n = 324
Z-score ≥ 2 , n (%)	113 (47.7)	27 (31.0)	140 (43.2)
LVPWd before or at MPS I diagnosis, n (%)	38 (16.0)	10 (11.5)	48 (14.8)
Z-score $\geq 2^{**}$, n (%)	11 (28.9)	2 (20.0)	13 (27.1)
IVSd			
	n = 205	n = 86	n = 291
Z-score ≥ 2 , n (%)	62 (30.2)	14 (16.3)	76 (26.1)
IVSd before or at MPS I diagnosis, n (%)	37 (18.0)	11 (2.8)	48 (16.5)
Z-score $\geq 2^{**}$, n (%)	9 (24.3)	1 (9.1)	10 (20.8)
LVEDd			
	n = 242	n = 95	n = 337
Z-score ≥ 2 , n (%)	67 (27.7)	9 (9.5)	76 (22.6)
LVEDd before or at MPS I diagnosis, n (%)	38 (15.7)	11 (11.6)	49 (14.5)
Z-score $\geq 2^{**}$, n (%)	14 (36.8)	1 (9.1)	15 (30.6)
LVEsD			
	n = 231	n = 90	n = 321
Z-score ≥ 2 , n (%)	75 (32.5)	7 (7.8)	82 (25.5)
LVEsD before or at MPS I diagnosis, n (%)	35 (15.2)	10 (11.1)	45 (14.0)
Z-score $\geq 2^{**}$, n (%)	13 (37.1)	1 (10.0)	14 (31.1)
Shortening fraction			
	n = 261	n = 104	n = 365
<28%, n (%)	42 (16.1)	7 (6.7)	49 (13.4)
Shortening fraction before or at MPS I diagnosis, n (%)	43 (16.5)	16 (15.4)	59 (16.2)
<28% ^{**} , n (%)	8 (18.6)	2 (12.5)	10 (16.9)

IVSd = intraventricular septal thickness in diastole, IQR = interquartile range, LVED = left ventricular end-diastolic dimension, LVEs = left ventricular end-systolic dimension, LVPWd = left ventricular posterior wall thickness in diastole, MPS I = mucopolysaccharidosis type I, SD = standard deviation.

*Chi-square test and non-parametric Wilcoxon tests were used to calculate p-values of percentage of valve dysfunction and age at first reported valve dysfunction, respectively, between severe and attenuated MPS I groups. The percentages were based on individuals with a usable response to the valve dysfunction (yes/no). Those with unknown or missing responses were excluded.

**Percent determined using number of individuals with any data before or at MPS I diagnosis as denominator

In contrast, estimated left ventricular chamber dimension Z-scores in both systole (Fig. 2C) and diastole (Fig. 2D) significantly decreased over time in the severe, but not the attenuated, phenotype, and the difference in slopes between the two groups was significant for both measurements ($p = 0.001$ and $p < 0.001$, respectively). Finally, mixed model analysis showed that shortening fractions were within normal limits over time (Fig. 2E) and increased (improved) over time in the severe phenotype while remaining unchanged in the attenuated phenotype (p -value for the difference by phenotype = 0.002).

Discussion

Cardiac abnormalities are common findings in individuals with mucopolysaccharidosis type I, but to date, the natural history of untreated cardiac features of the disease has not been well described, with reports limited to small numbers of patients, single institutions, or specific age groups or phenotypes. The data provided herein represent the largest natural history assessment of the cardiac features of untreated mucopolysaccharidosis type I from individuals of all age ranges and phenotypes gathered from sites throughout the globe. As such, it confirms some suspected findings of earlier, smaller studies and presents new and important information that may provide a useful benchmark with which to evaluate new therapies for the disease.

This study confirms that cardiac valve disease, particularly left-sided, is an early and common manifestation of both severe and attenuated disease and, though often presenting a decade earlier in the severe phenotype, is more prevalent in the attenuated phenotype. Mitral regurgitation and aortic regurgitation are the most frequently reported left-sided valve abnormalities in both severe and attenuated phenotypes and occur earlier than valve stenosis. Left-sided valve stenosis, by contrast, is more common in the older attenuated phenotype and seems to be confirmed by studies that show that valve replacement for attenuated mucopolysaccharidosis is performed almost universally for valve stenosis.⁴³ While the reason for this finding remains unclear, the contribution of ongoing valvular inflammation leading to fibrosis, and hence stenosis, such as is seen in chronic versus acute rheumatic mitral disease may provide some insight into the mechanism.⁴⁴

Right-sided valve dysfunction is much less common in both severe and attenuated mucopolysaccharidosis, except for tricuspid regurgitation. While the frequency of tricuspid valve regurgitation was high in both groups, the severity of regurgitation is not known in this study. Trivial regurgitation is present in many young individuals in the general population without clinical consequence.^{45,46}

Significant abnormalities of left ventricular dimension were more common in individuals with severe compared to attenuated disease. Hypertrophy of the left ventricular posterior wall and abnormal left ventricular end-diastolic dimension were the most frequent findings in both phenotypes, especially among younger individuals. For the small number of individuals with data prior to mucopolysaccharidosis diagnosis, posterior wall hypertrophy was present before diagnosis in 29% of these individuals. Hypertrophy of the posterior wall, rather than the interventricular septum, is unique to our study, as hypertrophy of the septum has previously been reported in other studies.^{18,25} Significantly smaller left ventricular chamber size has been reported in mucopolysaccharidosis type IV,⁴⁷ as was found in the individuals with severe mucopolysaccharidosis type I in our study and may be explained by the inward direction of hypertrophy resulting in decreased chamber diameters. Over time, little change in either left ventricular posterior wall hypertrophy or ventricular dimensions occurred in the attenuated phenotype. By contrast, among individuals with severe disease, posterior wall and septal thickness progressed while end-diastolic and -systolic dimensions decreased. Progressive hypertrophy may result from continued cardiac glycosaminoglycan accumulation that, in turn, results in diastolic dysfunction, a faster heart rate, and a smaller left ventricular dimension. For the severe phenotype, with little to no active alpha-L-iduronidase enzyme, this accumulation may occur more rapidly than in the attenuated phenotype, where enzyme levels may be

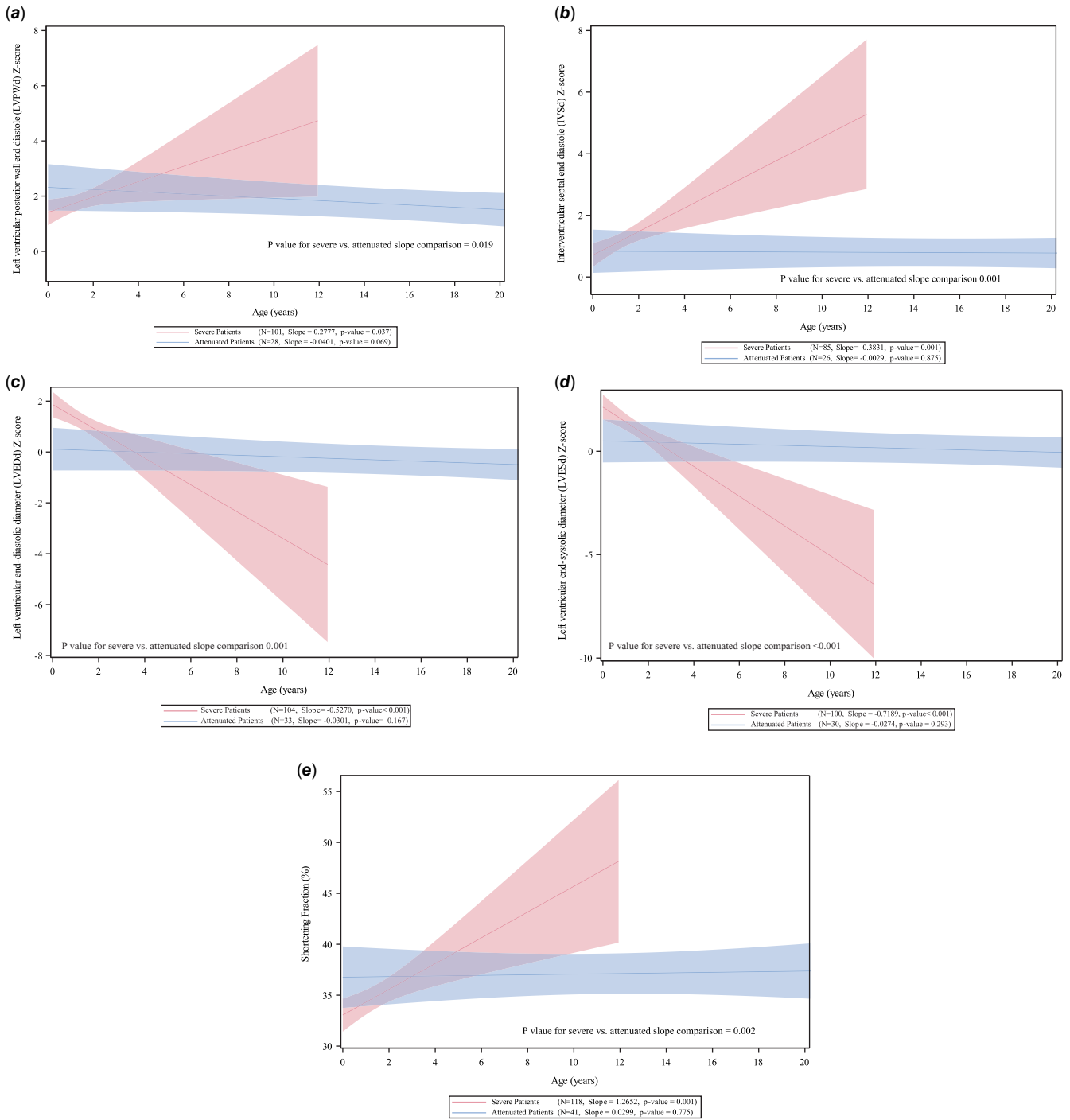


Figure 2. Estimated changes in chamber dimensions Z-scores and shortening fraction over time for individuals with severe and attenuated MPS I from mixed model analyses of patients with ≥ 2 echocardiogram measurements over time. The red and blue solid lines represent the estimated slopes for each parameter over time for the severe and attenuated groups, respectively. Shaded areas represent the 95% confidence bands. Legends below the figures include the number of individuals in each group, p-values for whether the slope is significantly different from 0, and the p-value for interaction indicating whether the slopes are different between the two groups. A. Z-scores for left ventricular posterior wall thicknesses in diastole. B. Z-scores for intraventricular septal thicknesses in diastole. C. Z-scores for left ventricular end-diastolic dimension. D. Z-scores for left ventricular end-systolic dimension. E. Shortening fraction.

higher. It is also feasible that septal hypertrophy may be overestimated in those with the severe phenotype, since these individuals are most often of short stature⁴⁸ and therefore have a lower body surface area for their age. Since the heart grows physiologically during childhood, the lower body surface area may overestimate hypertrophy.

Decreased cardiac left ventricular function (shortening fraction <28%) was uncommon but was observed more often in individuals with the severe compared to the attenuated phenotype. The highest percentage of decreased ventricular function occurred in the youngest group of individuals with severe disease (those <6 months of age). Decreased cardiac function in young infants

has previously been reported in both mucopolysaccharidosis type I^{39,49,50} and mucopolysaccharidosis type VI (Maroteaux-Lamy).⁵¹ In the era of newborn screening, decreased cardiac systolic function is of clinical importance. When averaged over all age groups, cardiac function remained within normal limits over time for both phenotypes, although statistically, shortening fraction improved over time for individuals with the severe phenotype but remained unchanged for those with attenuated disease.

The limitations of this study include the voluntary nature of registry data for which the frequency and type of assessments according to standard of care may be performed at irregular intervals. Echocardiographic data are submitted from institutions using different equipment, adhering to differing protocols, and with varying degrees of experience in performing and interpreting echocardiography from those with mucopolysaccharidosis. Inter-observer variability may result in significant errors, especially in the measurement of cardiac function and amount of valvular regurgitation.^{52,53} Due to the subjective nature of reporting cardiac valve regurgitation, only the presence or absence of the finding was included in this report. In addition, left ventricular function was assessed by shortening fraction rather than a volumetric quantification. The measurement of ejection fraction in infants and young children with mucopolysaccharidosis is challenging due to poor acoustic windows and lack of cooperation. As the data were retrospective and voluntary, we could not require ejection fraction (or sedation) to submit data. Although this measurement could strengthen the findings of this manuscript, these data were not consistently available to us, in part because the registry predates these recommendations by more than a decade. For the same reasons, measurements of Z-scores based on age, sex, race, and ethnicity, which may contribute to small differences in the data,⁵⁴ were not made. Cardiac data elements did not include other components of more recent interest such as aortic dimensions, aortic root dilation, strain, and diastolic function.

While there is less than a 4% transcription error of submitted data into the registry,⁵⁵ there is variability in data capture (e.g., use of handwritten notes versus full reports) and inability to assess how echocardiography was performed (i.e., according to current recommendations for standardisation of measurements). It is important to note that a challenge of performing echocardiograms in this population is the bony abnormalities of the sternum and ribs, which may yield inaccurate measurements for some individuals with severe disease. For example, 26% of respondents with severe disease had no valve dysfunction ever reported. Potential explanations for this finding include that individuals without valve dysfunction were younger than the overall group and had fewer echocardiographs, that valve findings were subtle or not investigated, or a combination of the above factors. The integrity of the data is supported by the finding that those who reported “yes” for valve dysfunction were older than those who reported “no” when the age of the first valve dysfunction was recorded, a finding compatible with the progressive nature of glycosaminoglycan storage in this disease. Finally, despite the large number of enrollees, some estimates of changes in parameters over time were based on a small number of data points. Any measurement error, either by echocardiography or by measurement of height and weight, could affect the findings from small numbers of individuals. While rare diseases registry-based data are extremely valuable to assess disease natural history and the impact of treatment, improvements in data capture, for example availability of actual echocardiographic imaging studies, will significantly aid in the interpretation of results.

With the availability of enzyme replacement therapy for attenuated disease and hematopoietic stem cell transplantation for severe disease in very young children,^{6,7} determining the natural history of untreated mucopolysaccharidosis has become unfeasible. The Mucopolysaccharidosis Type I Registry provides the opportunity to analyse the largest set of global longitudinal cardiac data available for individuals during treatment-naïve periods. Since most echocardiographs were obtained when colour Doppler was widely available, these Registry data likely provide an accurate assessment of the prevalence of valve dysfunction among treatment-naïve individuals.

Conclusions

Interrogation of echocardiograph data from a large international voluntary registry of individuals with mucopolysaccharidosis type I who are treatment-naïve has shown that left-sided cardiac valve disease is common. Mitral regurgitation is the most common valve dysfunction for severe and attenuated phenotypes, but left-sided valve stenosis is more common in those with attenuated disease. Hypertrophy of the left ventricular posterior wall develops early and progresses within the severe phenotype but remains stable in the attenuated phenotype. Decreased cardiac function, while uncommon, occurs in 25% of infants less than 6 months of age with the severe phenotype and is of clinical importance. Understanding the natural history of cardiac abnormalities will hopefully be useful for the clinical assessment of people living with mucopolysaccharidosis type I.

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Ethical standard. Written consent was required of all participants prior to enrolment in the registry. As of December 2012, each participating site has been required to have approval from an institutional review board or ethics committee for registry participation.

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