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Growth in individuals with attenuated mucopolysaccharidosis type I during untreated and treated periods: Data from the MPS I registry

Lynda E. Polgreen[1] | Luisa Bay[2] | Lorne A. Clarke[3] | Nathalie Guffon[4] | Simon A. Jones[5] | Joseph Muenzer[6] | Ana Lorena Flores[7] | Kathryn Wilson[7] | David Viskochil[8]

[1]The Lundquist Institute at Harbor-UCLA Medical Center, Torrance, California, USA

[2]Hospital Nacional de Pediatría J. P. Garrahan, Ciudad Autónoma de Buenos Aires, Buenos Aires, Argentina

[3]Department of Medical Genetics and the British Columbia Children's Hospital Research Institute, University of British Columbia, Vancouver, British Columbia, Canada

[4]Centre de Référence des Maladies Héréditaires du Métabolisme, Hôpital Femme Mère Enfant, Lyon, France

[5]St Mary's Hospital, Manchester University Foundation Trust, University of Manchester, Manchester, UK

[6]Department of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[7]Sanofi, Cambridge, Massachusetts, USA

[8]Department of Pediatrics, Division of Medical Genetics, University of Utah School of Medicine, Salt Lake City, Utah, USA

Correspondence
Lynda Polgreen, The Lundquist Institute at Harbor-UCLA, 1124 W. Carson Street, Liu Research Building, Torrance, CA 90502l, USA.
Email: lpolgreen@lundquist.org

Funding information
Sanofi

Abstract

Mucopolysaccharidosis Type I (MPS I) is caused by deficiency of α-L-iduronidase. Short stature and growth deceleration are common in individuals with the attenuated MPS I phenotype. Study objectives were to assess growth in individuals with attenuated MPS I enrolled in The MPS I Registry while untreated and after initiation of enzyme replacement therapy (ERT) with laronidase (recombinant human iduronidase). Individuals in the MPS I Registry with at least one observation for height and assigned attenuated MPS I phenotype as of September 2020 were included. The cohort included 142 males and 153 females 2–18 years of age. Age and sex adjusted standardized height-for-age *z*-scores during the natural history and ERT-treatment periods were assessed using linear mixed model repeated measures analyses. Growth curves were estimated during both periods and compared to standard growth charts from the Center for Disease Control (CDC). There was a significantly slower decline in height *z*-scores with age during the ERT-treated period compared to the natural history period. Estimated average height *z*-scores in the ERT-treatment versus the natural history period at age 10 were −2.4 versus −3.3 in females and −1.4 versus −2.9 in males (females first treated 3 year; males <4.1 year). While median height remained below CDC standards during both the natural history and ERT-treated periods for individuals with attenuated MPS I, laronidase ERT was associated with slower declines in height *z*-scores.

KEYWORDS
disease-specific growth curves, enzyme replacement therapy, lysosomal storage disorders, mucopolysaccharidosis

1 | INTRODUCTION

Glycosaminoglycan (GAG) homeostasis is important for normal skeletal development (Clarke, 2011). Consequently, growth failure is common in inherited metabolic disorders caused by genetic defects in GAG metabolism, including the mucopolysaccharidoses (MPS). GAG accumulation and secondary alterations in complex cellular pathways result in multi-systemic disease with variable disease course and a spectrum of clinical manifestations that include growth failure and short stature (Melbouci et al., 2018).

Mucopolysaccharidosis type I (MPS I) has an incidence of approximately 1/100,000 live births (Giugliani et al., 2017; Moore et al., 2008). Deficiency of α-L-iduronidase (IDUA) resulting in the accumulation of GAG substrates, dermatan and heparan sulfate, leads to progressive multisystem disease with a natural history spectrum ranging from severe (Hurler syndrome, OMIM 607014) to attenuated (Hurler-Scheie OMIM 607015 and Scheie syndromes, OMIM 607016). Enzyme replacement therapy (ERT) with the recombinant human IDUA laronidase (Aldurazyme) is FDA and EMEA approved for MPS I. Laronidase is well tolerated, and treatment not only decreases urinary GAG levels, but also improves respiratory function, physical capacity, and organomegaly (Kakkis et al., 2001; Wraith, 2005; Wraith et al., 2004). As MPS I is a progressive multisystem disorder, the benefit of ERT appears to be most pronounced when treatment is initiated in the early stages of the disease natural history (Gabrielli et al., 2016; Wraith et al., 2007).

Growth failure and short stature are common in MPS disorders, as are other bone and skeletal manifestations (Morishita & Petty, 2011; Müller et al., 2021; Rozdzynska-Swiatkowska et al., 2015; Tylki-Szymanska et al., 2010; Vijay & Wraith, 2005). In untreated individuals with attenuated MPS I, disease-specific growth charts show that growth deviates from reference curves by 2 years of age and median height is below the third percentile by 9 years of age (Guffon et al., 2019; Viskochil et al., 2019). There are limited data available regarding the impact of ERT on longitudinal growth in individuals with attenuated MPS I. Data from an open-label study of laronidase showed that growth rate increased by 35%–192% in five children age 8–12 years with attenuated MPS I after 1 year of treatment (Kakkis et al., 2001). In a 1-year study, three of four children with attenuated MPS I showed a net increase in height-for-age *z*-scores after initiation of laronidase treatment (Wraith et al., 2007). Other studies in small numbers of patients suggest that ERT has a positive impact on height, especially if initiated early in the disease natural history (Al-Sannaa et al., 2015; Laraway et al., 2016; Sifuentes et al., 2007; Wraith et al., 2007). In contrast, one study of 14 individuals showed no significant impact of ERT on height, regardless of the age when ERT was initiated (Tylki-Szymanska et al., 2010).

The purpose of this study was to assess growth responses after initiation of ERT in individuals with attenuated MPS I enrolled in the MPS I Registry.

2 | METHODS

2.1 | Ethical standards

Institutional review boards or ethics committees at all study sites approved the study. Patients and/or their parents/guardians provided written informed consent in compliance with local regulations.

2.2 | Study design

Data were obtained from The MPS I Registry (NCT00144794), an observational global longitudinal database funded by Sanofi (Cambridge, MA) and established to capture standard of care clinical and biochemical assessments of patients with MPS I and to evaluate clinical outcomes. Individuals are referred to the MPS I Registry by their clinician and participate voluntarily. Data are collected both retro- and prospectively as previously described (Pastores et al., 2007). A Board of Advisors comprised of physicians oversee the Registry that is sponsored by Sanofi.

2.3 | Study population

Patients in the MPS I Registry with attenuated disease, known birth date, known treatment status, and, among treated patients, known date of first ERT treatment were eligible for inclusion in the analysis (Table 1). Data reported from the initiation of the Registry in 2003 through September 2020 were included; some data are from measurements performed prior to 2003 since the Registry allows retrospective data entry. Patients were included if they had at least one height measurement between ages 2 and 18 years entered in the Registry, and all available height observations during that age period were included in the analysis.

2.4 | Analysis

Data were stratified by sex and age for the analysis of height observations classified by treatment period. The natural history period includes measurements from up to 6 months after the first ERT treatment. The ERT-treated period includes measurements from 6 months onward after the first treatment. Because most patients had multiple height observations over time, they could contribute data to one or both periods. Height measurements were determined to be outliers and excluded if they were evaluated as biologically implausible (i.e., height measurements ≤90 cm from age 5 to <10 years, and ≤100 cm from age 10 to <18 years), or if the change from the previous measurement resulted in a growth rate of more than 25 cm/year or a decrease of more than 25 cm/year.

Descriptive analyses were performed with means, standard deviations, medians and 25% and 75% percentiles determined for continuous variables, and percent for categorical variables. Age- and sex-

TABLE 1 Characteristics of MPS I registrants with height/length measurements[a]

		Males $N = 142$[b]		Females $N = 153$[b]	
	Overall $N = 295$	Natural history period $N = 110$	ERT-treated period $N = 107$	Natural history period $N = 130$	ERT-treated period $N = 120$
Number of records, *n*	2704	394	926	439	945
2003[c] or earlier, *n* (%)	445 (16.5)	199 (50.5)	5 (0.5)	213 (48.5)	28 (3.0)
After 2003, *n* (%)	2259 (83.5)	195 (49.5)	921(99.5)	226 (51.5)	917 (97.0)
Age at MPS I diagnosis, year					
Mean (SD)	5.6 (4.1)	5.8 (4.0)	4.9 (3.4)	6.0 (4.3)	4.8 (3.4)
Median (25th, 75th)	4.5 (3.1, 7.5)	4.6 (3.2,7.3)	4.1 (2.9,6.2)	4.9 (3.2,8.4)	4.1 (2.3,6.5)
Age at first ERT treatment, year					
Mean (SD)	9.3 (6.3)		7.1 (4.3)		7.9 (4.1)
Median (25th, 75th)	7.9 (4.6, 12.7)	NA	5.7 (4.1, 9.4)	NA	7.7 (4.4, 11.0)
Natural history follow-up time, year					
Mean (SD)	2.0 (3.0)	2.1 (3.4)	NA	1.9 (2.6)	NA
Median (25th, 75th)	0.6 (0.0, 3.0)	0.6 (0.0, 2.5)		0.6 (0.0, 3.2)	
ERT-treated follow-up time, year					
Mean (SD)	4.4 (3.8)	NA	4.5 (4.0)	NA	4.3 (3.6)
Median (25th, 75th)	3.4 (1.4, 7.2)		3.3 (1.4, 7.4)		3.5 (1.4, 7.0)
Age at first height measurement within specified period, year					
Mean (SD)	7.5 (4.4)	7.1 (4.5)	8.8 (4.6)	7.3 (4.1)	9.4 (4.2)
Median (25th, 75th)	6.3 (3.8, 10.7)	5.7 (3.5, 9.8)	7.6 (5.2, 13.0)	6.4 (3.9, 10.0)	9.3 (5.7, 12.8)
Age at last height measurement within specified period, year					
Mean (SD)	9.8 (4.8)	9.3 (4.9)	13.3 (4.4)	9.2 (4.3)	13.7 (4.1)
Median (25th, 75th)	9.4 (5.5, 14.0)	8.0 (4.8, 14.3)	14.7 (9.9, 17.3)	8.6 (5.3, 11.9)	15.2 (11.1, 17.1)
Geographic region *n* (%)					
JAPAC	7 (2.4)	2 (1.4)		5 (3.3)	
Europe	146 (49.5)	62 (43.7)		84 (54.9)	
North America	96 (32.5)	51 (35.9)		45 (29.4)	
Latin America	46 (15.6)	27 (19.0)		19 (12.4)	

Abbreviation: NA, not applicable.

[a]Includes only records with physiologically plausible data as described in Section 2.

[b]Of the 142 males, 35 contributed height records only to the Natural History period, 32 contributed only to the ERT-treated period, and 75 contributed to both. Of the 153 females, 33 contributed height records only to the Natural History period, 23 contributed only to the ERT-treated period, and 97 contributed to both.

[c]Laronidase ERT was introduced in 2003.

stratified standardized growth data were used from the Centers for Disease Control (CDC) growth charts (DepartmentHHS, 2002). Height-for-age *z*-scores (the number of standard deviations from the reference population) were determined using normative growth data from the CDC (https://www.cdc.gov/growthcharts/cdc_charts.htm). Individuals with *z*-scores greater than two standard deviations below the mean (i.e., *z*-scores ≤ -2) were considered to have short stature.

Height *z*-scores over time and investigation of rate of change in *z*-scores for the natural history versus ERT-treated periods were assessed using linear mixed effects models to account for repeated measures over time. *z*-Scores were calculated based on CDC growth charts. The age range included in these models was cut off when there were fewer than 10 height records for either the natural history or ERT-treated groups in a given year, resulting in an age range for

TABLE 2 Linear mixed model estimates for height *z*-score[a] based on age and treatment status. Linear mixed model regression coefficients for the age-related terms predicting height *z*-score, by sex

Parameter	# patients	# height records	Estimate	SE	*p*-value	95% CI lower limit	95% CI upper limit
Males, age 3 to <18 years	138	1282	-	-	-	-	-
Age, per 1 year increase[b]	-	-	−0.335	0.0511	<0.0001	−0.435	−0.234
Age-squared, per 1 unit increase[b]	-	-	0.010	0.0030	0.0013	0.004	0.016
Age × Treatment Interaction[c]	-	-	0.281	0.0461	<0.0001	0.190	0.371
Age-squared × Treatment Interaction[c]	-	-	−0.012	0.0027	<0.0001	−0.017	−0.007
Females, age 3 to <13 years	133	914	-	-	-	-	-
Age, per 1 year increase[b]	-	-	−0.545	0.0646	<0.0001	−0.672	−0.417
Age-squared, per 1 unit increase[b]	-	-	0.026	0.0054	<0.0001	0.016	0.037
Age × Treatment interaction[c]	-	-	0.315	0.0609	<0.0001	0.196	0.435
Age-squared × Treatment interaction[c]	-	-	−0.021	0.0043	<0.0001	−0.030	−0.013

Notes: The terms "Age × Treatment Interaction" and "Age-squared × Treatment Interaction" reflect the difference in height *z*-scores over time for ERT-treated patients compared to natural history patients (i.e., the referent group). In addition to the age-related terms presented in the table, the final models are also adjusted for age at diagnosis (in quartiles) and age at first treatment (for ERT-treated observations only; in quartiles for males and continuous years for females). The final models included random effects for the intercept (*z*-score at age 3), age, and age-squared (with age in years shifted to age −3, the start of the age range in the models). The models used an unstructured covariance matrix and were estimated using restricted maximum likelihood. The full difference in predicted *z*-scores for ERT-treated versus natural history at a given age will depend on the coefficients for "age × treatment interaction" and "age-squared × treatment interaction" and the coefficient for the age at first treatment of the ERT-treated patient (estimates not shown). Age at first treatment was parameterized differently for males and females based on selecting the model with the lowest Akaike information criterion (AIC) separately for each group. In addition to the fixed effects included in the final models, we also considered models adjusting for: Region (Europe/Middle East/Africa, North America, Latin America, Japan/Asia-Pacific); age at diagnosis without age at first treatment, and vice versa; and age at diagnosis and age at first treatment parameterized as quartiles or as continuous variables. We also considered models with and without age-squared terms. The final models presented above reflect those with the lowest AIC values for males and females.

Abbreviations: CI, confidence interval; SE, standard error.

[a]Height-for-age *z*-score calculated based on age in months at height measurements using US CDC growth charts.

[b]Age = (age in years −3), i.e., shifted to begin at 3 years, which is the start of the age range included in the models.

[c]Interaction terms reflect the additional change in *z*-score per 1-unit increase in age or age-squared for patients receiving ERT.

males of 3 to <18 years, and for females of 3 to <13 years. An unstructured covariance matrix was used, and models were estimated using restricted maximum likelihood. The final models included random effects for the intercept (*z*-score at age 3), age, and age-squared (with age in years shifted to age −3, the start of the age range in the models), and included fixed effects for age, age-squared, and the interactions of age and age-squared by treatment status (i.e., ERT-treated vs. natural history observations). The age-squared variables allow the model to reflect the association between age and height *z*-scores during childhood/adolescence more accurately, rather than assuming a linear change in *z*-scores across all ages. The interaction of age (modeled as age and age-squared) with treatment status allows the association between age and height *z*-scores to differ between natural history and ERT-treated measurements. Models also included fixed effects for age at diagnosis (in quartiles for both males and females) and age at first treatment (in quartiles for males; continuous years for females; based on model fit), because both covariates are associated with height and treatment status. Final models were selected based on minimizing the Akaike Information Criterion (AIC); additional details on final models and model selection are included in Table 2.

The General Additive Models for Location Scale and Shape (GAMLSS) package for R statistical software (https://www.gamlss.com/) (Rigby & Stasinopoulos, 2005) was used to estimate growth curves separately for the natural history and ERT-treated height-by-age data, stratified by sex. Growth curves were estimated for the same age ranges as were used for the *z*-score models described above. The Box-Cox normal, Box-Cox t, and Box-Cox power exponential distributions (all with log-links for mu and cubic splines for smoothing) were compared to select the best-fitting model for each group, based on minimizing the value of the generalized AIC (GAIC). The median, 3rd, and 97th percentile curves based on the selected model for each group were plotted and compared to CDC growth curves.

3 | RESULTS

3.1 | Participants and characteristics

Among 425 individuals classified with attenuated disease in the MPS I Registry, 26 were excluded because of treatment with HSCT and 103 were excluded due to absence of height records. After review for outlier data, the final study population consisted of 295 individuals with 2704 height records. Growth curve and modeling analyses

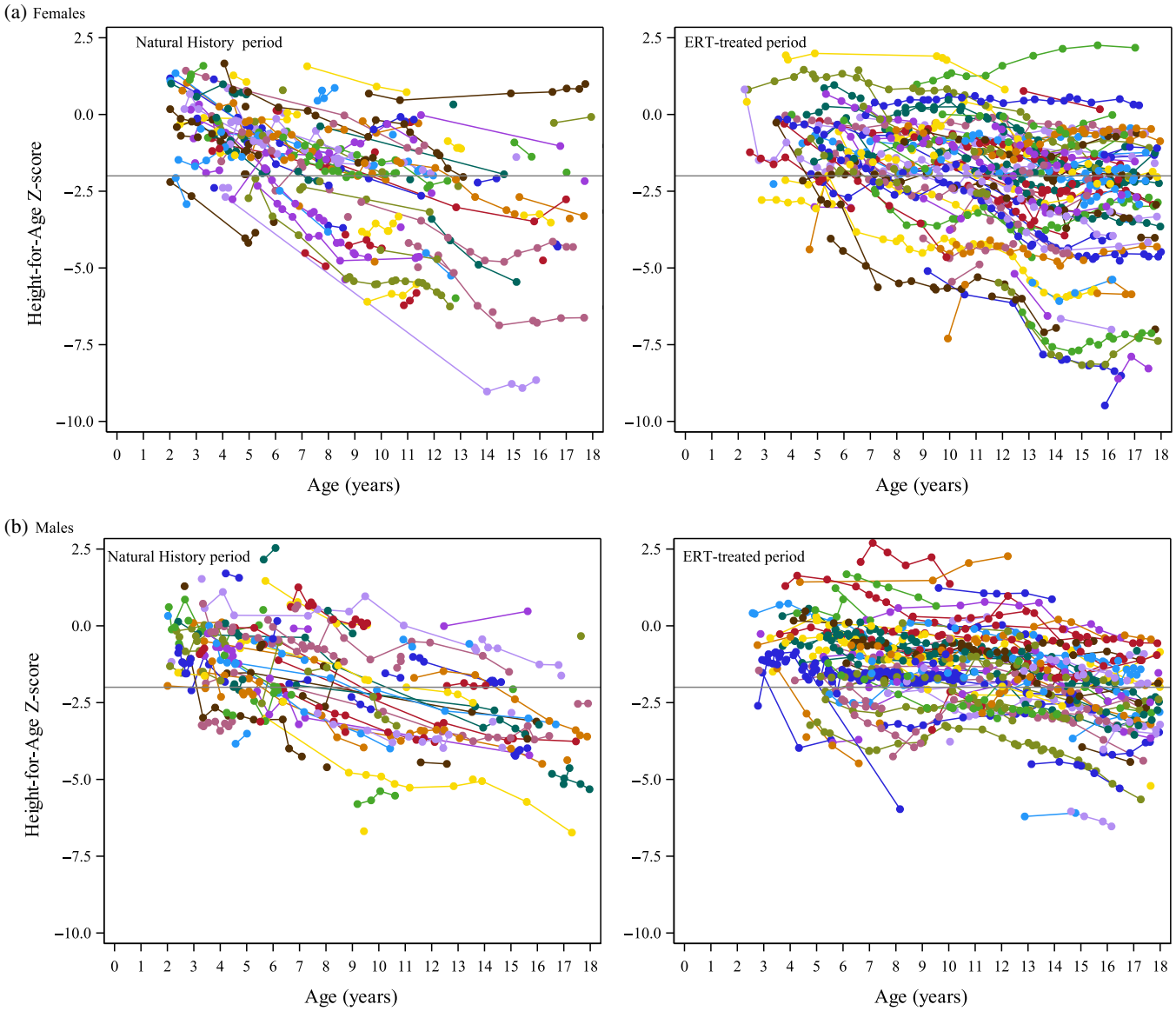

FIGURE 1 *Z*-scores by age. Individual height-for-age *z*-scores for females (a) and males (b) with attenuated MPS I during the natural history and ERT-treated periods. Data for females is based on 130 people with 439 height measurements for the natural history period and 120 people with 945 measurements for the ERT-treated period. Data for males is based on 110 people with 394 height measurements for the natural history period and 107 people with 926 height measurements for the ERT-treated period. Height-for-age *z*-scores were calculated based on age in months at height measurements using US CDC growth charts. Horizontal gray line indicates the *z*-score two standard deviations below the mean (−2.0)

excluded records for individuals <3 years and analyses for females were truncated at 13 years since there were fewer than 10 available height records for the natural history period after that age resulting in analysis population of 273 individuals with 2198 height records.

Table 1 shows participant characteristics, median follow-up times, and the median ages at diagnosis stratified by sex and treatment period. Among 142 males, 110 had data during the natural history period and 107 during the ERT-treated period. Among 153 females, 130 had data during the natural history period and 120 during the ERT-treated period. Of the 142 males, 35 contributed height records only to the natural history period, 32 contributed only to the ERT-treated period, and 75 contributed to both. Of the 153 females, 33 contributed height records only to the natural history period, 23 contributed records only to the ERT-treated period, and 97 contributed to both. Approximately half of the natural history records were from 2003 or earlier whereas almost all (>99% for males, 97% for females) height records for the ERT-treated period occurred after 2003 reflecting approval of laronidase in 2003. Most individuals (82%) were from either Europe or North America, and 18% were from either Japan/Asia-Pacific or Latin America.

Median ages at MPS I diagnosis and median follow-up times were generally similar by sex. Median age (25th,75th percentile) at ERT

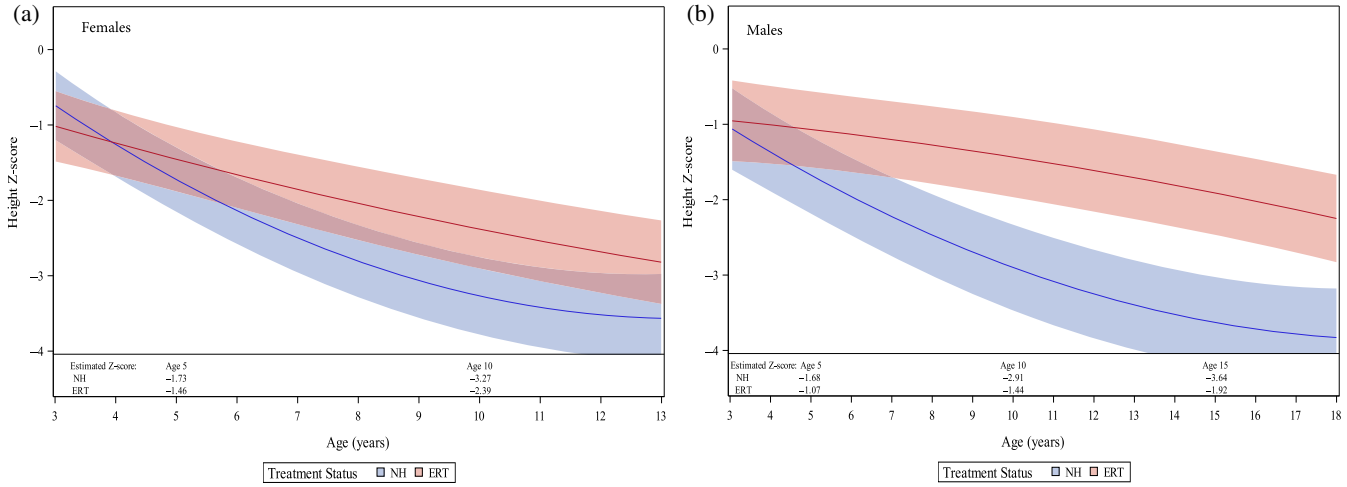

FIGURE 2 Impact of ERT treatment on height *z*-scores. Linear mixed model repeated measures analyses of growth during the natural history (NH, blue line) and ERT-treated periods (ERT, red line) for females (a), $N = 133$ with 914 height records and males (b), $N = 138$ with 1282 height records. 95% confidence intervals are indicated by blue and red shading. See Table 2 for additional information. The representative curves are for individuals diagnosed in the earliest quartile of age at diagnosis (before age 3.2 years for boys, 2.6 years for girls). The ERT-treated curves are for individuals first treated at age 3. Embedded tables are the estimated height *z*-scores for the indicated ages. Results were similar for different ages at diagnosis and treatment cutoffs (Table 3)

initiation in the ERT-treated group was 2 years later in females compared to males (7.7 [4.4, 11.0] years vs. 5.7 [4.1, 9.4] years, respectively), and varied by region: 7.7 (4.3, 10.9) years versus 5.1 (4.1, 10.6) years for females and males, respectively, in Europe; 8.1 (3.4, 9.4) years versus 5.6 (2.3, 8.1) years for females and males, respectively, in Latin America; and 7.4 (5.0, 12.1) years versus 7.4 (4.3, 9.7) years for females and males, respectively in North America.

3.2 | Height-for-age *z*-scores

Individual height-for-age *z*-scores are shown for females (Figure 1a) and males (Figure 1b) with attenuated MPS I during the natural history and ERT-treated periods. To determine rate of change in *z*-scores for the natural history versus ERT-treated periods and account for variation in ages at diagnosis and treatment onset, linear mixed models of estimated *z*-scores over time were generated. Representative estimated height *z*-scores over time for the natural history and ERT-treated periods are shown in Figure 2 for females (a) and males (b). The age-squared variables were highly significant ($p < 0.0001$) in all models, suggesting that the decrease in height *z*-scores for individuals with MPS I was not linear throughout childhood. There was a significantly slower decline in *z*-scores with age during the ERT-treated period compared to the natural history period in both males and females (*p*-values for interactions between treatment status and age [modeled as age and age-squared] were <0.0001 for both sexes (Table 2). The embedded table on each figure shows the *z*-scores for representative ages based on the models. Within the designated time frames, the estimated *z*-scores for the ERT group were less negative relative to *z*-scores during the natural history period for individuals of the same age. Results were similar for different ages at diagnosis and first treatment as shown in Table 3. Table 3 also lists the age at which short stature (*z*-score ≤ −2) is estimated to occur for females and males in the different age at diagnosis and age at first treatment groupings. Consistently in both sexes, the age at which short stature is estimated to occur is later during the ERT-treated period than during the natural history period.

3.3 | MPS I height-for-age plots for females and males with attenuated MPS I disease

Estimated growth trajectories for the natural history and ERT-treated periods for females and males plotted against CDC reference growth curves are shown in Figure 3. For both males and females, median growth (50th percentile) is below the CDC reference median in both natural history and ERT-treated periods.

For females, median height during the natural history period was similar to the CDC third percentile for height from age 8 through 12 years of age (Figure 3a). During the ERT-treated period (Figure 3b), median height remained above the CDC third percentile until 12 years of age. Median heights at 13 years of age during the natural history and ERT periods were between 135 and 140 cm. Individual subject height data from the natural history and ERT-treated periods for females are shown in Figure S1 and individual data overlaid on CDC growth curves are shown in Figure S3.

In males (Figure 3c), median height for the natural history period fell below the CDC third percentile at approximately 9 years of age. During the ERT-treated period (Figure 3d) the age at which median growth fell below the CDC third percentile was between 14 and 15 years. The median height achieved at 18 years of age was approximately 155 cm compared to 145 cm during the natural history period.

TABLE 3 Linear mixed model estimates of height *z*-scores over time, for patients with different ages at diagnosis and first treatment

Females	Estimated *z*-score (95% confidence interval) at age		Age when estimated *z*-score is −2
	5 years	10 years	
Diagnosed <2.6 years (Quartile 1)			
Untreated	−1.73 (−2.16, −1.31)	−3.27 (−3.79, −2.76)	5.7
ERT-treated, age at first treatment 3 year	−1.46 (−1.89, −1.03)	−2.39 (−2.91, −1.86)	7.8
Diagnosed 2.6 to <4.4 years (Quartile 2)			
Untreated	−1.03 (−1.44, −0.62)	−2.57 (−3.09, −2.06)	7.7
ERT-treated, age at first treatment 5 year	−0.94 (−1.37, −0.52)	−1.87 (−2.36, −1.39)	10.9
Diagnosed 4.4 to <7.5 years (Quartile 3)			
Untreated	-	−2.25 (−2.74, −1.76)	8.9
ERT-treated, age at first treatment 7 year	-	−1.73 (−2.21, −1.26)	11.8
Diagnosed 7.5 years or later (Quartile 4)			
Untreated	-	−1.93 (−2.47, −1.38)	10.5
ERT-treated, age at first treatment 10 year	-	−1.69 (−2.24, −1.13)	12.1

Males	Estimated z-score (95% confidence interval) at age			Age when estimated *z*-score is −2
	5 years	10 years	15 years	
Diagnosed <3.2 years (Quartile 1)				
Untreated	−1.68 (−2.19, −1.16)	−2.91 (−3.48, −2.34)	−3.64 (−4.24, −3.03)	6.2
ERT-treated, age at first treatment <4.1 year (Quartile 1)	−1.07 (−1.57, −0.56)	−1.44 (−1.97, −0.91)	−1.92 (−2.47, −1.36)	15.8
Diagnosed from 3.2 to <4.5 years (Quartile 2)				
Untreated	−1.08 (−1.57, −0.59)	−2.31 (−2.84, −1.78)	−3.04 (−3.60, −2.48)	8.6
ERT-treated, age at first 4.1 to <5.7 year (Quartile 2)	−1.26 (−1.76, −0.75)	−1.63 (−2.14, −1.11)	−2.11 (−2.64, −1.57)	14.1
Diagnosed 4.5 to <6.6 years (Quartile 3)				
Untreated	-	−2.06 (−2.57, −1.54)	−2.79 (−3.33, −2.24)	9.8
ERT-treated, age at first treatment 5.7 to <9.4 year (Quartile 3)	-	−1.57 (−2.08, −1.06)	−2.05 (−2.58, −1.52)	14.6
Diagnosed 6.6 years or later (Quartile 4)				
Untreated	-	−2.14 (−2.67, −1.61)	−2.87 (−3.40, −2.33)	9.4
ERT-treated, age at first treatment ≥9.4 year (Quartile 4)	-	−1.96 (−2.52, −1.40)	−2.44 (−2.98, −1.90)	10.6

Notes: The linear mixed models adjust for age at diagnosis and age at first treatment. The model for females is adjusted for quartiles of age at diagnosis and, for treated estimates, continuous age at first treatment. The age at first treatment used are the medians for age at first treatment for each quartile of age at diagnosis. The model for females was based on observations from age 3 through 13, so estimates for *z*-score at age 15 are not presented. The model for males is adjusted for quartiles of age at diagnosis and, for treated estimates, for quartiles of age at first treatment.

Individual subject height data from the natural history and ERT-treated periods for males are shown in Figure S2 and individual data overlaid on CDC growth curves for the natural history and ERT-treated periods are shown in Figure S4.

4 | DISCUSSION

Few large studies have evaluated the long-term impact of laronidase ERT on growth of individuals with attenuated MPS I. In other MPS disorders, studies suggest that ERT has a positive impact on growth compared to untreated individuals (Cho et al., 2014; Harmatz et al., 2017; Jones et al., 2013; Patel et al., 2014; Schulze-Frenking et al., 2011). Data from the MPS I Registry provide the opportunity to assess longitudinal growth in large numbers of individuals during both untreated and ERT-treated time periods. Our results indicate a positive association between ERT and growth in patients with attenuated MPS I and support findings from laronidase clinical trials and case studies (Al-Sannaa et al., 2015; Kakkis et al., 2001; Laraway et al., 2016; Sifuentes et al., 2007; Wraith et al., 2007).

Estimates of median growth during both the natural history and ERT-treated periods were significantly below CDC standard growth curves, and height *z*-scores declined over time in both periods. Data interpretation and the ability to draw conclusions based on unadjusted growth curve or *z*-score data are confounded by varying ages at MPS I diagnosis and ERT initiation, and due to some individuals in

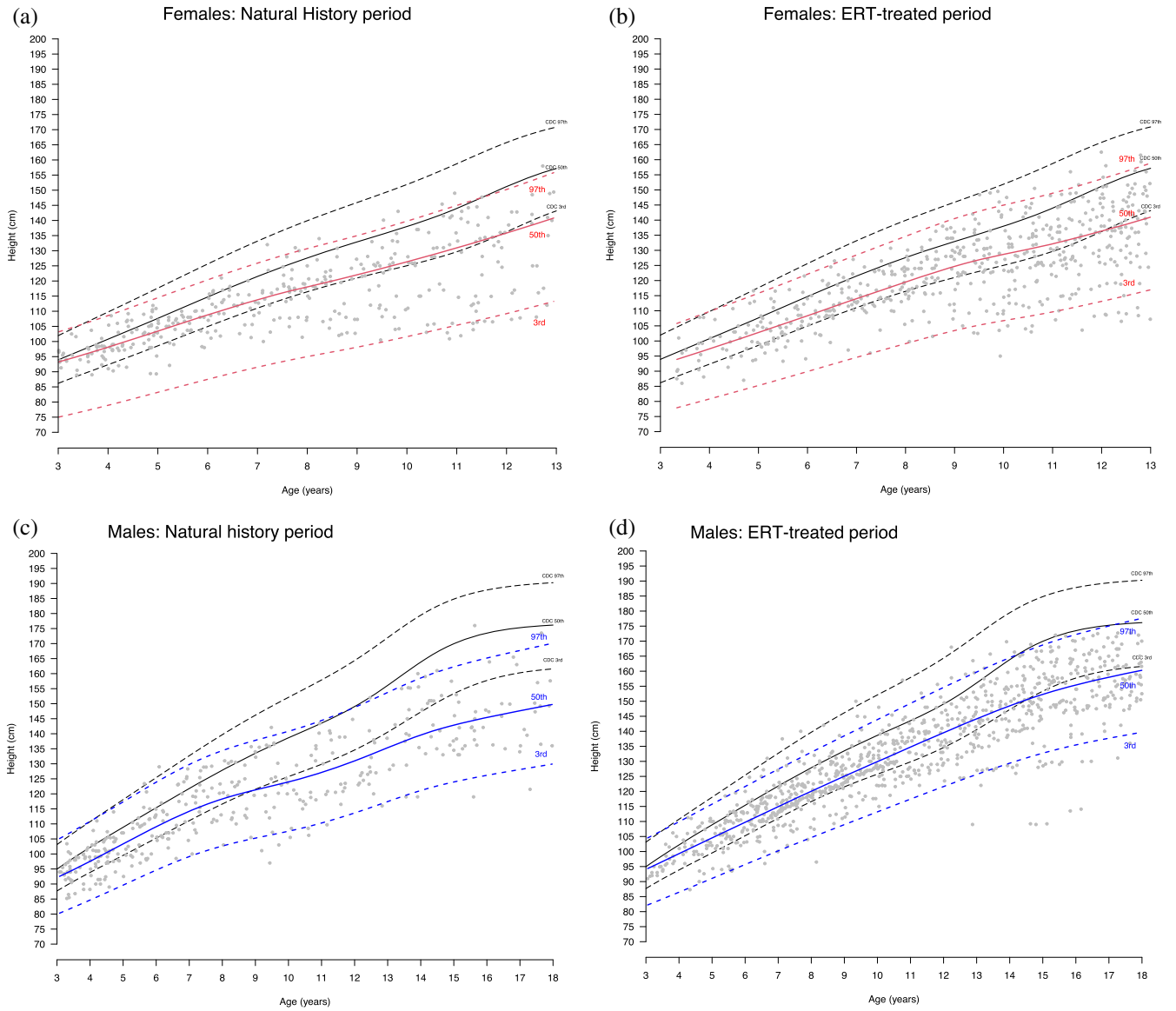

FIGURE 3 Estimated height growth trajectories for individuals with attenuated MPS I. Estimated growth trajectories from MPS I registry data for females (red) during the natural history period (a) or ERT-treated period (b) and males (blue) during the natural history period (c) or ERT-treated period (d) overlaid on CDC standard curves. CDC median and 97th and 3rd percentiles curves are shown in black. Individual data points are indicated by gray circles

the Registry having only single data points while others had multiple height measurements. Therefore, linear mixed modeling was used to adjust for multiple variables including age at diagnosis and age at first treatment and accounted for varying numbers of height measurements per individual, to determine whether *z*-scores differed between the natural history and ERT-treated periods. The models showed that height *z*-scores decreased over time in both the natural history and ERT-treated periods. However, during the period that individuals received laronidase, the decline in *z*-scores was significantly slower than in the natural history period, and short stature, when it occurred, was at a later age.

The magnitude of the abatement in height *z*-score decline over time was less pronounced in females than in males. For the earliest diagnosis and treatment group (by 3–4 years of age) the estimated ages at which short stature (i.e., *z*-score ≤ −2.0) occurred in the ERT-treated group was >15 years for males compared to 8 years for females, versus <6 years of age for both sexes in the natural history period. Other than smaller numbers of natural history observations for females, it is not clear why the results differ by sex. One possibility could be differences in age at initiation of ERT. We observed that while ages at diagnosis were similar for males and females, females had a later onset of ERT initiation compared to males (by up to 2 years on average), particularly in some geographic regions. The linear mixed effects models for *z*-scores provided adjustments for both age at diagnosis and age at first treatment, but the study was not specifically designed to assess the impact of early laronidase treatment on

growth. However, in both females and males, later age at first treatment was associated with worse growth. Previous studies suggest that earlier treatment with laronidase can have a greater impact on outcomes, including growth. A case study of two siblings with attenuated MPS I showed that linear growth rate was normalized in a child who began ERT at the age of 5 months (97th percentile for height at 12 years) in contrast to a sibling who began ERT at the age of 5 years (10th percentile for height at 17 years) (Gabrielli et al., 2016). Similarly, in an assessment of nine sibships where younger siblings were diagnosed and treated earlier (Al-Sannaa et al., 2015), the majority of older siblings had attained height *z*-scores greater than two standard deviations below the mean (*z*-score < −2) while those for younger siblings were closer to the mean, and at comparable ages the heights of the younger siblings were greater than those of their older siblings. Another potential factor contributing to the sex differences is the limited numbers of observations for females compared to males and that data analyses for females could only be made up to age 13 compared to age 18 for males. Suboptimal pubertal growth spurts and growth cessation at age 13 have been described for untreated females with attenuated MPS I and attenuated MPS IV (Guffon et al., 2019).

The impact of ERT on growth observed in the current analysis is likely to be the result of multiple factors, including both direct and indirect effects of decreased GAG accumulation with alterations of signal transduction pathways, modulation of cytokines and other inflammatory mediators, and alteration of the intracellular targeting pathways, endocytosis, apoptosis, and autophagy (Clarke, 2011; Kingma & Jonckheere, 2021). GAG storage triggers a complex pathogenic cascade of abnormal biological mechanisms, and MPS animal models have shown early abnormalities of chondrocyte organization in the growth plate and architecture of cortical bone (Heppner et al., 2015; Holley et al., 2011; Silveri et al., 1991; Simonaro et al., 2001; Wilson & Bromme, 2010). The transformation of cartilage into bone is disrupted by GAG accumulation in chondroblasts and is an early manifestation of MPS that alters normal bone growth and impacts final height (Jiang et al., 2020; Müller et al., 2021).

In the absence of randomized controlled studies, the MPS I Registry provides a valuable source of international, longitudinal data for individuals with both severe and attenuated disease. The limitations of this retrospective study are inherent to registry-based data analysis, including the lack of randomization between individuals in the natural history and ERT-treated groups, and the greater number of records available during the ERT-treated period compared to the natural history period. There were potential variations in height measurements due to use of different methods at each clinical site, although it is expected that within each center multiple observations from a single individual resulted in reasonably accurate reporting of longitudinal data. Our height estimates were also only compared to CDC growth charts, which might not fully reflect standards for an international patient cohort. Limitations of the analysis also include the limited data during the natural history period in older teen years for females and at age 3 years or less for both sexes. No data were available regarding Tanner stage or secondary sex traits in the population and growth related to puberty or potential therapies for growth failure were not assessed. Individuals with MPS I may experience pubertal failure, as well as precocious puberty (Gardner et al., 2011; Polgreen & Miller, 2010), and initiation of ERT prior to puberty has been shown to have a substantial impact on growth compared to starting ERT after puberty (Sifuentes et al., 2007). Also, joint contractures and spinal deformities have been reported for participants in the MPS I registry (Beck et al., 2014) and likely play a role in final height determinations for individuals with MPS I. While early ERT may impact progression of skeletal abnormalities (Al-Sannaa et al., 2015), these clinical manifestations may also vary among MPS I patients by geographic region (Munoz-Rojas et al., 2011). In our study, the impact of spinal abnormalities or contractures of the hips and knees on height were not assessed. Finally, MPS I Registry data were limited for individuals from Asia-Pacific and Latin America, although sites in other regions including Asia, Latin America and the Middle East have recently opened to enhance representation from other ethnic groups in the Registry, but these data were not available for the current analyses.

We found that growth is improved but not normalized with ERT in individuals with attenuated MPS I. Short stature remains a common manifestation even with long-standing ERT use. Additional understanding of persistent growth plate and other skeletal abnormalities may provide insight to pathways important for optimization of growth in individuals with attenuated MPS I. Based on our findings, there is a need for early ERT, and adjunctive therapies focused on improving growth in individuals with attenuated MPS I. We anticipate optimization of the effects of ERT on final height with implementation of newborn screening for MPS I and subsequent interventions early in the disease process. Understanding the impact of ERT on growth and final height is important information for physicians, patients, and caregivers. Growth charts presented here can be used as a reference in clinical practice to interpret an individual patient's response to ERT.

5 | CONCLUSION

In conclusion, this study represents a large comparative analysis of longitudinal growth patterns during natural history and ERT-treated periods for individuals with attenuated MPS I and suggests that ERT with laronidase has a positive impact on height.

AUTHOR CONTRIBUTIONS

Lynda E. Polgreen, David Viskochil, Lorne A. Clarke, Luisa Bay, Kathryn Wilson, Simon A. Jones, Joseph Muenzer, Nathalie Guffon, and Ana Lorena Flores participated in the development of the study, interpretation of data, and drafting/revision of the manuscript. In addition, KW performed statistical analyses. All authors read and approved the final manuscript.

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CONFLICTS OF INTEREST

Lynda Polgreen: Recipient of research support speaker's fees for educational events related to MPS from Sanofi. David Viskochil: Member of the International MPS I Registry advisory board, and recipient of honoraria, consulting fees, and travel reimbursement from Sanofi. Lorne A Clarke: Member of the International MPS I Registry advisory board and recipient of speaker's fees for educational events related to lysosomal disease from Sanofi. Luisa Bay: Member of the International MPS I Registry advisory board and recipient of honoraria, consulting fees, and travel reimbursement from Sanofi. Simon Jones: Principal investigator in Sanofi sponsored trials and recipient of honoraria and consulting fees from Sanofi. Nathalie Guffon: Member of the International MPS I Registry advisory board and recipient of honoraria and travel reimbursement from Sanofi. Ana Lorena Flores and Kathryn Wilson: Employees of Sanofi and may hold or have held stock options. Joseph Muenzer: Member of the International MPS I Registry advisory board and recipient of consulting fees from Sanofi. Kathryn Wilson is a contractor for Navitas Life Sciences and is funded by Sanofi.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Lynda E. Polgreen https://orcid.org/0000-0002-2881-6138
Lorne A. Clarke https://orcid.org/0000-0003-0512-7281
David Viskochil https://orcid.org/0000-0001-5364-3366

REFERENCES

Al-Sannaa, N. A., Bay, L., Barbouth, D. S., Benhayoun, Y., Goizet, C., Guelbert, N., Jones, S. A., Kyosen, S. O., Martins, A. M., Phornphutkul, C., Reig, C., Pleat, R., Fallet, S., & Ivanovska Holder, I. (2015). Early treatment with laronidase improves clinical outcomes in patients with attenuated MPS I: A retrospective case series analysis of nine sibships. *Orphanet Journal of Rare Diseases*, *10*(1), 131–139. https://doi.org/10.1186/s13023-015-0344-4

Beck, M., Arn, P., Giugliani, R., Muenzer, J., Okuyama, T., Taylor, J., & Fallet, S. (2014). The natural history of MPS I: Global perspectives from the MPS I registry. *Genetics in Medicine*, *16*(10), 759–765. https://doi.org/10.1038/gim.2014.25

Cho, S. Y., Huh, R., Chang, M. S., Lee, J., Kwun, Y., Maeng, S. H., Kim, S. J., Sohn, Y. B., Park, S. W., Kwon, E. K., Han, S. J., Jung, J., & Jin, D. K. (2014). Impact of enzyme replacement therapy on linear growth in Korean patients with mucopolysaccharidosis type II (Hunter syndrome). *Journal of Korean Medical Science*, *29*(2), 254–260. https://doi.org/10.3346/jkms.2014.29.2.254

Clarke, L. A. (2011). Pathogenesis of skeletal and connective tissue involvement in the mucopolysaccharidoses: Glycosaminoglycan storage is merely the instigator. *Rheumatology (Oxford)*, *50*(Suppl 5), 13–18. https://doi.org/10.1093/rheumatology/ker395

DepartmentHHS. (2002). 2000 CDC growth charts for the United States: Methods and development: Data from the National Examination Surveys and the National Health and Nutrition Examination Surveys. *Vital and Health Statistics Series 11, No. 246*. Hyattsville, MD: National Center for Health Statistics.

Gabrielli, O., Clarke, L. A., Ficcadenti, A., Santoro, L., Zampini, L., Volpi, N., & Coppa, G. V. (2016). 12 year follow up of enzyme-replacement therapy in two siblings with attenuated mucopolysaccharidosis I: The important role of early treatment. *BMC Medical Genetics*, *17*(1), 19. https://doi.org/10.1186/s12881-016-0284-4

Gardner, C. J., Robinson, N., Meadows, T., Wynn, R., Will, A., Mercer, J., Church, H. J., Tylee, K., Wraith, J. E., & Clayton, P. E. (2011). Growth, final height and endocrine sequelae in a UKpopulation of patients with Hurler syndrome (MPS1H). *Journal of Inherited Metabolic Disease*, *34*(2), 489–497. https://doi.org/10.1007/s10545-010-9262-8

Giugliani, R., Federhen, A., Michelin-Tirelli, K., Riegel, M., & Burin, M. (2017). Relative frequency and estimated minimal frequency of lysosomal storage diseases in Brazil: Report from a reference laboratory. *Genetics and Molecular Biology*, *40*(1), 31–39. https://doi.org/10.1590/1678-4685-GMB-2016-0268

Guffon, N., Journeau, P., Brassier, A., Leger, J., & Chevallier, B. (2019). Growth impairment and limited range of joint motion in children should raise suspicion of an attenuated form of mucopolysaccharidosis: Expert opinion. *European Journal of Pediatrics*, *178*(4), 593–603. https://doi.org/10.1007/s00431-019-03330-x

Harmatz, P., Hendriksz, C. J., Lampe, C., McGill, J. J., Parini, R., Leao-Teles, E., Valayannopoulos, V., Cole, T. J., Matousek, R., Graham, S., Guffon, N., & Quartel, A. (2017). The effect of galsulfase enzyme replacement therapy on the growth of patients with mucopolysaccharidosis VI (Maroteaux-Lamy syndrome). *Molecular Genetics and Metabolism*, *122*, 107–112. https://doi.org/10.1016/j.ymgme.2017.03.008

Heppner, J. M., Zaucke, F., & Clarke, L. A. (2015). Extracellular matrix disruption is an early event in the pathogenesis of skeletal disease in mucopolysaccharidosis I. *Molecular Genetics and Metabolism*, *114*(2), 146–155. https://doi.org/10.1016/j.ymgme.2014.09.012

Holley, R. J., Deligny, A., Wei, W., Watson, H. A., Ninonuevo, M. R., Dagalv, A., Leary, J. A., Bigger, B. W., Kjellén, L., & Merry, C. L. (2011). Mucopolysaccharidosis type I, unique structure of accumulated heparan sulfate and increased N-sulfotransferase activity in mice lacking alpha-L-iduronidase. *The Journal of Biological Chemistry*, *286*(43), 37515–37524. https://doi.org/10.1074/jbc.M111.287474

Jiang, Z., Byers, S., Casal, M. L., & Smith, L. J. (2020). Failures of endochondral ossification in the mucopolysaccharidoses. *Current Osteoporosis Reports*, *18*(6), 759–773. https://doi.org/10.1007/s11914-020-00626-y

Jones, S. A., Parini, R., Harmatz, P., Giugliani, R., Fang, J., & Mendelsohn, N. J. (2013). The effect of idursulfase on growth in patients with Hunter syndrome: Data from the hunter outcome survey (HOS). *Molecular Genetics and Metabolism*, *109*(1), 41–48. https://doi.org/10.1016/j.ymgme.2013.03.001

Kakkis, E. D., Muenzer, J., Tiller, G. E., Waber, L., Belmont, J., Passage, M., Izykowski, B., Phillips, J., Doroshow, R., Walot, I., Hoft, R., & Neufeld, E. F. (2001). Enzyme-replacement therapy in mucopolysaccharidosis I. *The New England Journal of Medicine*, *344*(3), 182–188. https://doi.org/10.1056/NEJM200101183440304

Kingma, S. D. K., & Jonckheere, A. I. (2021). MPS I: Early diagnosis, bone disease and treatment, where are we now? *Journal of Inherited Metabolic Disease*, *44*(6), 1289–1310. https://doi.org/10.1002/jimd.12431

Laraway, S., Mercer, J., Jameson, E., Ashworth, J., HensmanDip, P., & Jones, S. A. (2016). Outcomes of long-term treatment with laronidase in patients with mucopolysaccharidosis type I. *The Journal of Pediatrics*, *178*, 219–226.e1. https://doi.org/10.1016/j.jpeds.2016.08.033

Melbouci, M., Mason, R. W., Suzuki, Y., Fukao, T., Orii, T., & Tomatsu, S. (2018). Growth impairment in mucopolysaccharidoses. *Molecular Genetics and Metabolism*, *124*(1), 1–10. https://doi.org/10.1016/j.ymgme.2018.03.004

Moore, D., Connock, M. J., Wraith, E., & Lavery, C. (2008). The prevalence of and survival in mucopolysaccharidosis I: Hurler, Hurler-Scheie and Scheie syndromes in the UK. *Orphanet Journal of Rare Diseases*, *3*, 24–30. https://doi.org/10.1186/1750-1172-3-24

Morishita, K., & Petty, R. E. (2011). Musculoskeletal manifestations of mucopolysaccharidoses. *Rheumatology (Oxford)*, *50*(Suppl 5), v19–v25. https://doi.org/10.1093/rheumatology/ker397

Müller, F., Alomar, K., & Journeau, P. (2021). Musculoskeletal anomalies in children with mucopolysaccaridoses. *Journal of Genij Ortopedii*, *27*(4), 446–449.

Munoz-Rojas, M. V., Bay, L., Sanchez, L., van Kuijck, M., Ospina, S., Cabello, J. F., & Martins, A. M. (2011). Clinical manifestations and treatment of mucopolysaccharidosis type I patients in Latin America as compared with the rest of the world. *Journal of Inherited Metabolic Disease*, *34*(5), 1029–1037. https://doi.org/10.1007/s10545-011-9336-2

Pastores, G. M., Arn, P., Beck, M., Clarke, J. T., Guffon, N., Kaplan, P., Muenzer, J., Norato, D. Y. J., Shapiro, E., Thomas, J., Viskochil, D., & Wraith, J. E. (2007). The MPS I registry: Design, methodology, and early findings of a global disease registry for monitoring patients with mucopolysaccharidosis type I. *Molecular Genetics and Metabolism*, *91*(1), 37–47. https://doi.org/10.1016/j.ymgme.2007.01.011

Patel, P., Suzuki, Y., Tanaka, A., Yabe, H., Kato, S., Shimada, T., Mason, R. W., Orii, K. E., Fukao, T., Orii, T., & Tomatsu, S. (2014). Impact of enzyme replacement therapy and hematopoietic stem cell therapy on growth in patients with Hunter syndrome. *Molecular Genetics and Metabolism Reports*, *1*, 184–196. https://doi.org/10.1016/j.ymgmr.2014.04.001

Polgreen, L. E., & Miller, B. S. (2010). Growth patterns and the use of growth hormone in the mucopolysaccharidoses. *Journal of Pediatric Rehabilitation Medicine*, *3*(1), 25–38. https://doi.org/10.3233/prm-2010-0106

Rigby, R. A., & Stasinopoulos, D. M. (2005). Generalized additive models for location, scale and shape (with discussion). *Applied Statistics*, *54*, 507–554.

Rozdzynska-Swiatkowska, A., Jurecka, A., Cieslik, J., & Tylki-Szymanska, A. (2015). Growth patterns in children with mucopolysaccharidosis I and II. *World Journal of Pediatrics*, *11*(3), 226–231. https://doi.org/10.1007/s12519-014-0517-6

Schulze-Frenking, G., Jones, S. A., Roberts, J., Beck, M., & Wraith, J. E. (2011). Effects of enzyme replacement therapy on growth in patients with mucopolysaccharidosis type II. *Journal of Inherited Metabolic Disease*, *34*(1), 203–208. https://doi.org/10.1007/s10545-010-9215-2

Sifuentes, M., Doroshow, R., Hoft, R., Mason, G., Walot, I., Diament, M., Okazaki, S., Huff, K., Cox, G. F., Swiedler, S. J., & Kakkis, E. D. (2007). A follow-up study of MPS I patients treated with laronidase enzyme replacement therapy for 6 years. *Molecular Genetics and Metabolism*, *90*(2), 171–180. https://doi.org/10.1016/j.ymgme.2006.08.007

Silveri, C. P., Kaplan, F. S., Fallon, M. D., Bayever, E., & August, C. S. (1991). Hurler syndrome with special reference to histologic abnormalities of the growth plate. *Clinical Orthopaedics and Related Research*, Aug (269), 305–311.

Simonaro, C. M., Haskins, M. E., & Schuchman, E. H. (2001). Articular chondrocytes from animals with a dermatan sulfate storage disease undergo a high rate of apoptosis and release nitric oxide and inflammatory cytokines: A possible mechanism underlying degenerative joint disease in the mucopolysaccharidoses. *Laboratory Investigation*, *81*(9), 1319–1328.

Tylki-Szymanska, A., Rozdzynska, A., Jurecka, A., Marucha, J., & Czartoryska, B. (2010). Anthropometric data of 14 patients with mucopolysaccharidosis I: Retrospective analysis and efficacy of recombinant human alpha-L-iduronidase (laronidase). *Molecular Genetics and Metabolism*, *99*(1), 10–17. https://doi.org/10.1016/j.ymgme.2009.08.008

Vijay, S., & Wraith, J. E. (2005). Clinical presentation and follow-up of patients with the attenuated phenotype of mucopolysaccharidosis type I. *Acta Paediatrica*, *94*(7), 872–877. https://doi.org/10.1080/08035250510031584

Viskochil, D., Clarke, L. A., Bay, L., Keenan, H., Muenzer, J., & Guffon, N. (2019). Growth patterns for untreated individuals with MPS I: Report from the international MPS I registry. *American Journal of Medical Genetics. Part A*, *179*(12), 2425–2432. https://doi.org/10.1002/ajmg.a.61378

Wilson, S., & Bromme, D. (2010). Potential role of cathepsin K in the pathophysiology of mucopolysaccharidoses. *Journal of Pediatric Rehabilitation Medicine*, *3*(2), 139–146. https://doi.org/10.3233/prm-2010-0116

Wraith, J. E. (2005). The first 5 years of clinical experience with laronidase enzyme replacement therapy for mucopolysaccharidosis I. *Expert Opinion on Pharmacotherapy*, *6*(3), 489–506. https://doi.org/10.1517/14656566.6.3.489

Wraith, J. E., Beck, M., Lane, R., van der Ploeg, A., Shapiro, E., Xue, Y., Kakkis, E. D., & Guffon, N. (2007). Enzyme replacement therapy in patients who have mucopolysaccharidosis I and are younger than 5 years: Results of a multinational study of recombinant human alpha-L-iduronidase (laronidase). *Pediatrics*, *120*(1), e37–e46. https://doi.org/10.1542/peds.2006-2156

Wraith, J. E., Clarke, L. A., Beck, M., Kolodny, E. H., Pastores, G. M., Muenzer, J., Rapoport, D. M., Berger, K. I., Swiedler, S. J., Kakkis, E. D., Braakman, T., Chadbourne, E., Walton-Bowen, K., & Cox, G. F. (2004). Enzyme replacement therapy for mucopolysaccharidosis I: A randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase). *The Journal of Pediatrics*, *144*(5), 581–588. https://doi.org/10.1016/j.jpeds.2004.01.046

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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