Molecular Genetics and Metabolism 117 (2016) 438–446

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

The natural history of growth in patients with Hunter syndrome: Data from the Hunter Outcome Survey (HOS)

Rossella Parini [a,*], Simon A. Jones [b], Paul R. Harmatz [c], Roberto Giugliani [d], Nancy J. Mendelsohn [e,f]

[a] Rare Metabolic Disease Unit, Pediatric Department, University Milano Bicocca, San Gerardo Hospital, Via Pergolesi 33, 20900 Monza, Italy
[b] Willink Unit, Manchester Centre for Genomic Medicine, St Mary's Hospital, Manchester Academic Health Sciences Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK
[c] UCSF Benioff Children's Hospital Oakland, Oakland, CA 94609, USA
[d] Medical Genetics Service/HCPA, Department of Genetics/UFRGS and INAGEMP, Rua Ramiro Barcelos 2350, 90035-903 Porto Alegre, RS, Brazil
[e] Department of Medical Genetics, Children's Hospitals and Clinics of Minnesota, 2525 Chicago Ave South, CSC 560, Minneapolis, MN 55404, USA
[f] Department of Pediatrics, Division of Genetics, University of Minnesota, Minneapolis, MN 55455, USA

ARTICLE INFO

Article history:
Received 28 November 2015
Received in revised form 23 January 2016
Accepted 23 January 2016
Available online 25 January 2016

Keywords:
Head circumference
Lysosomal storage disease
Mucopolysaccharidosis type II
Weight
Height
Puberty

ABSTRACT

Hunter syndrome (mucopolysaccharidosis type II) affects growth but the overall impact is poorly understood. This study investigated the natural history of growth and related parameters and their relationship with disease severity (as indicated by cognitive impairment). Natural history data from males followed prospectively in the Hunter Outcome Survey registry and not receiving growth hormone or enzyme replacement therapy, or before treatment start, were analysed (N = 676; January 2014). Analysis of first-reported measurements showed short stature by 8 years of age; median age-corrected standardized height score (z-score) in patients aged 8–12 years was −3.1 (1st, 3rd quartile: −4.3, −1.7; n = 68). Analysis of growth velocity using consecutive values found no pubertal growth spurt. Patients had large head circumference at all ages, and above average body weight and body mass index (BMI) during early childhood (median z-score in patients aged 2–4 years, weight [n = 271]: 1.7 [0.9, 2.4]; BMI [n = 249]: 2.0 [1.1, 2.7]). Analysis of repeated measurements over time found greater BMI in those with cognitive impairment than those without, but no difference in height, weight or head circumference. Logistic regression modelling (data from all time points) found that increased BMI was associated with the presence of cognitive impairment (odds ratio [95% CI], 3.329 [2.313–4.791]), as were increased weight (2.365 [1.630–3.433]) and head circumference (1.749 [1.195–2.562]), but not reduced height. Unlike some other MPS disorders, there is no evidence at present for predicting disease severity in patients with Hunter syndrome based on changes in growth characteristics.

1. Introduction

Hunter syndrome (or mucopolysaccharidosis type II [MPS II]; OMIM# 309900)[1] is a rare and life-limiting X-linked recessive lysosomal storage disease. The disorder is caused by deficient activity of the enzyme iduronate-2-sulfatase (EC 3.1.6.13) that is responsible for breaking down the glycosaminoglycans (GAGs) heparan and dermatan sulfate within lysosomes [1]. Estimates of birth prevalence range from approximately 1 in 50,000 live male births in Taiwan [2] and 1 in 77,000 newborn boys in Europe [3, 4] to 1 in 162,000 newborn boys in Australia [5]. Girls are affected only rarely [6]. Disease-related signs and symptoms typically begin in infancy and are progressive and multisystemic in nature, affecting the skin and mucosae, bones and joints, upper and lower airways, eyes and hearing, heart, liver and spleen, and central and peripheral nervous systems [1]. Clinical presentation is highly heterogeneous. Although disease severity covers a wide continuum, for clinical purposes patients are typically considered to fall into one of two categories: those with severe or attenuated disease. The severe form is characterized by central nervous system (CNS) involvement with progressive cognitive impairment; early onset of disease and severe somatic manifestations are also typical [7–9]. Individuals with the attenuated form remain cognitively intact. However, in contrast to MPS I for example, patients with the attenuated form of Hunter syndrome display somatic involvement that can range from severe and early onset to much less severe with later onset [7–9]. Thus, cognitive impairment and severe somatic manifestations do not always follow a parallel course in Hunter syndrome. All patients have reduced life expectancy [10].

* Corresponding author.
E-mail addresses: rossella.parini@unimib.it (R. Parini), simon.jones@cmft.nhs.uk (S.A. Jones), pharmatz@mail.cho.org (P.R. Harmatz), rgiugliani@hcpa.edu.br (R. Giugliani), Nancy.Mendelsohn@childrensmn.org (N.J. Mendelsohn).

[1] BMI, body mass index; CI, confidence interval; CNS, central nervous system; ERT, enzyme replacement therapy; GAG, glycosaminoglycan; GH, growth hormone; HOS, Hunter Outcome Survey; JROM, joint range of motion; MPS, mucopolysaccharidosis; OR, odds ratio; SD, standard deviation.

http://dx.doi.org/10.1016/j.ymgme.2016.01.009
1096-7192/

Individuals with Hunter syndrome are generally larger and heavier from birth to around 3 years of age than their non-affected peers [9, 11, 12]. In addition, growth velocity has been reported to be greater in the first years of life, before decreasing to below that of the reference population and becoming close to zero, even during puberty [13]. The height deficit becomes clearly apparent during the first decade [6–9, 11, 14–16]. The limited data that are available from several studies also indicate that patients with Hunter syndrome typically develop a larger head circumference and are heavier than healthy individuals [7–9, 11, 12, 14]. However, the impact of Hunter syndrome on growth is generally poorly understood and requires better characterization. An analysis of the effects of enzyme replacement therapy in a large population of patients enrolled in the Hunter Outcome Survey (HOS) registry confirmed that a height deficit typically becomes apparent in untreated patients from approximately 8 years of age, and suggested that there may be no pubertal growth spurt [17]. Nonetheless, questions remain regarding whether there is any association between growth-related manifestations of Hunter syndrome and aspects such as disease severity and neurological involvement, and whether patients experience a normal or near-normal pubertal growth spurt or not.

This analysis aimed to investigate the natural history of height, weight, body mass index (BMI) and head circumference in the large group of patients with Hunter syndrome enrolled in HOS, and to determine whether there is an association between growth and related parameters and disease severity.

2. Materials and methods

2.1. Survey design

HOS is a global, multicentre, longitudinal, observational registry that collects data on the natural history of Hunter syndrome and long-term safety and effectiveness of enzyme replacement therapy (ERT) with idursulfase (Elaprase®, Shire, Lexington, MA, USA). All patients with a confirmed diagnosis of Hunter syndrome are eligible for enrolment in the registry. Each participating centre obtained approval from its local Ethics Committee or Institutional Review Board before enrolling patients. Written informed consent for participation was provided by each patient, their parents or a legal representative. As well as collecting data on patients followed prospectively, retrospective data can be entered on patients who died before enrolment.

Information, including demographic and clinical data, on patients followed prospectively in the registry is collected from assessment at HOS entry and at subsequent routine clinic visits at intervals determined to be necessary by the treating physician. Data from historical evaluations of these patients may also be recorded. Data entry was conducted as described previously [14]. Quality control checks are performed in conjunction with data analyses. All patient information is managed in accordance with national data protection standards.

2.2. Patient populations and data collection

As of January 2014, 970 patients were enrolled in HOS, from 118 clinics in 26 countries. Of these patients, 817 were followed prospectively in the registry. This analysis included all natural history data for male patients followed prospectively in HOS who had not received idursulfase, and all available data up to 3 months after the start of treatment for those receiving idursulfase therapy. This time point was chosen because any effects of idursulfase on growth are not expected to clinically manifest for at least 3 months. Patients who had received growth hormone (GH) treatment at any time were excluded from all analyses, as were those for whom it was not recorded whether or not they had received GH treatment.

HOS collects information on parameters related to growth retrospectively and at subsequent routine clinic visits after entry into HOS. Height, weight and head circumference are measured according to standard clinical practice at each centre. BMI was calculated from height and weight measurements using the standard formula: BMI (kg/m^2) = weight (kg) / (height [m])^2 [18]. Data on concomitant medications (including GH therapy) are collected at the same time points as other measurements. The presence of musculoskeletal manifestations such as contractures, joint stiffness and spine and bone deformities at the time of enrolment in HOS was recorded.

For the purposes of this analysis, the extent of disease severity was determined based on the presence or absence of cognitive involvement, which in turn was based on the answer to the question 'Cognitive impairment: yes/no' in HOS for the period from birth to HOS entry and at subsequent visits. Assessment of cognitive impairment by the healthcare provider was by clinical impression and/or standardized testing. Patients for whom the presence of cognitive impairment was recorded at any time were considered to have cognitive involvement.

2.3. Data analysis

The first-reported raw data values for height, weight and BMI were plotted against reference data for boys from the USA Centers for Disease Control [19]. BMI reference data were available only from 2 years of age. Raw head circumference data were plotted against Nellhaus reference data [20]. Cubic regression was used to fit the curves to the HOS data. Age-corrected standardized scores (z-scores; the number of standard deviations [SDs] from the reference population mean) were calculated for weight and height for predefined age groups from 2 to 20 years of age. Data are presented as median with first and third quartiles unless otherwise specified.

Height velocity was also analysed, to investigate when boys with Hunter syndrome start to exhibit a reduced growth rate and whether they experience a pubertal growth spurt. To obtain meaningful data for the calculation of height velocity from the height measurements available in HOS (recorded at unequal intervals during routine clinical practice), only consecutive values having a minimum of 3 months' and a maximum of 2 years' difference were included in this part of the analysis. Height velocity was calculated using these data and the middle point between the consecutive values was used as the 'age at height velocity'. Outlying values, defined as those >20 cm/year, were excluded. All remaining data points were plotted on a scatterplot (865 values from 275 patients), with the Tanner normal curve included for reference [21].

Two forms of regression analysis were used to determine whether there was an association between cognitive involvement and abnormal parameters of growth: repeated measures analysis to examine the overall change over time, and logistic regression modelling using data from all time points, with occurrence of an extreme value of a growth parameter at least once as a covariate.

In the repeated measurements analysis, data from the subset of patients with at least three measurements available were used. Analyses using mixed models for repeated measurements were used to fit to the growth data over time. Linear, quadratic and cubic terms for age and interaction with the 'Cognitive impairment: yes/no' variable were included in the model to characterize the relationship between physical growth and age over time. The differences in least-squares means and standard errors were summarized.

Individual logistic regression modelling analyses were conducted for each variable using data from all time points. Growth parameter data for the modelling were grouped as follows: (i) height, at least one measurement less than the 5th centile from normal; (ii) weight (first analysis), at least one measurement less than the 5th centile from normal; (iii) weight (second analysis), at least one measurement greater than the 95th centile from normal; (iv) BMI, at least one measurement greater than the 95th centile from normal; (v) head circumference, at least one measurement more than 2 SDs above normal. In the models, the presence or absence of cognitive impairment was used as the outcome and the growth parameter as the factor. Associations were expressed

using odds ratios (ORs; 'Cognitive impairment: yes' over 'Cognitive impairment: no') and 95% confidence intervals (CIs). Individual analyses were conducted for each parameter.

3. Results

3.1. Patient population

Overall, 676 patients were included in this analysis (median age at last visit, 12.0 years; first and third quartile, 7.5 and 17.9 years). Of these, 322 were classified as having cognitive impairment and 336 were considered to have no cognitive impairment (Table 1; information missing for 18 patients). Overall, the median age at diagnosis was 3.3 (2.0; 4.9) years. Age at diagnosis was slightly lower in those with cognitive impairment than in those without: 3.0 (2.0; 4.1) and 3.8 (2.0; 5.8) years, respectively. Median age at HOS entry was 8.3 (4.5; 14.1) years and was also lower in those with cognitive impairment (7.7 [4.6; 12.2] years) than in those without (9.9 [4.2; 16.9] years). Median age at last cognitive assessment was 11.1 (7.0; 16.6) years; this was also lower in those with cognitive impairment (10.7 [7.2; 14.7] years) than in those without (12.2 [6.5; 19.9] years). Skeletal manifestations were recorded as being present before HOS entry in 90.2% of the overall patient population, and in 93.5% and 89.0% of those with and without cognitive impairment, respectively. In total, 21.0% (142/676) of the overall patient group in this analysis were recorded as having entered puberty (median age at first-reported puberty, 14.2 [9.3; 20.1] years). Information on 'Puberty: yes/no' was missing for 26.6% of patients. The proportion of individuals recorded as having entered puberty was similar in those with cognitive impairment (20.8%; information missing for 21.4%) and those without cognitive impairment (22.0%; information missing for 28.3%).

3.2. Analysis of the natural history of growth

Descriptive data for first measures of height, weight, BMI and head circumference in patients in this analysis are shown in Fig. 1; z-scores by age group are summarized in Table 2. Cross-sectional analysis of height showed that short stature relative to non-affected peers was apparent by 8 years of age (Fig. 1a; median z-score in patients aged 8–12 years, −3.1).

Patients were typically heavier than their non-affected peers until approximately 9 years of age, whereas older patients weighed substantially less than their peers (Fig. 1b; median z-score in patients aged 12–16 years and 16–20 years, −2.8 and −3.7, respectively). BMI was above average throughout childhood until approximately 14–16 years of age (Fig. 1c; median z-score did not exceed 2.0 for any age group). Patients in HOS generally had above-average head circumferences at all ages (Fig. 1d).

Analysis of growth velocity using consecutive measures revealed a decrease in growth rate from approximately 2.5 years, dropping below the lower limit of normal at approximately 7 years of age (Fig. 2). This analysis showed no evidence of a pubertal growth spurt.

3.3. Regression analysis and the association of cognitive impairment with abnormal parameters of growth

Regression curves of data from the subset of patients with at least three measurements available indicated that patients with cognitive impairment were slightly shorter than those without cognitive impairment; however, this difference was not considered clinically significant, and both groups of patients had short stature from the age of approximately 8 years (Fig. 3a). This analysis did not find any difference in weight between the two groups (Fig. 3b). However, whilst BMI was above average in both groups of patients (Fig. 3c), those with cognitive impairment had a greater BMI than those without cognitive impairment. This difference was apparent from a very young age and was maintained until at least 19 years of age. There was no difference in head circumference between those with and those without cognitive impairment (Fig. 3d). Head circumference was generally large, returning to near-normal when patients were in their mid-teens.

However, logistic regression modelling using data from all time points indicated an association between the presence of cognitive impairment and occurrence of increased weight at least once (OR, 2.365 [95% CI, 1.630–3.433]), BMI (3.329 [2.313–4.791]) and head circumference (1.749 [1.195–2.562]), but not reduced height (0.947 [0.669–1.339]) (Table 3).

4. Discussion

This is the first comprehensive analysis of the natural history of growth-related parameters and their relationship with disease severity in a large number of patients of many nationalities with Hunter syndrome. Our results demonstrated short stature after approximately 8 years of age, large head circumference at all ages and increased body weight and BMI during early childhood, supporting previous reports that were generally from smaller, country-specific populations [9, 11–13, 17]. In addition, we performed a formal analysis of growth velocity that demonstrated a drop in growth rate from the age of

Table 1
Demographics and baseline characteristics of patients in this analysis.

N		Overall	'Cognitive impairment: yes'[a]	'Cognitive impairment: no'[a]
		676	322	336
Age at onset of symptoms, years	Median (Q1; Q3)	1.5 (0.8; 3.0)	1.2 (0.6; 2.4)	2.0 (1.0; 3.5)
	n	552	284	260
Age at diagnosis, years	Median (Q1; Q3)	3.3 (2.0; 4.9)	3.0 (2.0; 4.1)	3.8 (2.0; 5.8)
	n	650	316	320
Delay between onset of symptoms and diagnosis, years	Median (Q1; Q3)	1.1 (0.3; 2.7)	1.2 (0.3; 2.7)	1.0 (0.2; 2.7)
	n	547	283	256
Age at last visit, years	Median (Q1; Q3)	12.0 (7.5; 17.9)	11.6 (7.9; 15.3)	13.1 (7.2; 20.6)
	n	676	322	336
Age at HOS entry, years	Median (Q1; Q3)	8.3 (4.5; 14.1)	7.7 (4.6; 12.2)	9.9 (4.2; 16.9)
	n	676	322	336
Age at last cognitive evaluation reported in HOS, years	Median (Q1; Q3)	11.1 (7.0; 16.6)	10.7 (7.2; 14.7)	12.2 (6.5; 19.9)
	n	658	322	336
Any skeletal manifestation before HOS entry	n (%)	610/676 (90.2)	301/322 (93.5)	299/336 (89.0)
Entered puberty (as recorded in HOS)	Yes (%)	142 (21.0)	67 (20.8)	74 (22.0)
	No (%)	354 (52.4)	186 (57.8)	167 (49.7)
	Missing (%)	180 (26.6)	69 (21.4)	96 (28.3)
	n	676	322	336

HOS, Hunter Outcome Survey; N/A, not applicable; Q1, first quartile; Q3, third quartile.
[a] Information on cognitive impairment was missing for 18 patients; data from these patients are not included in these columns of the table.

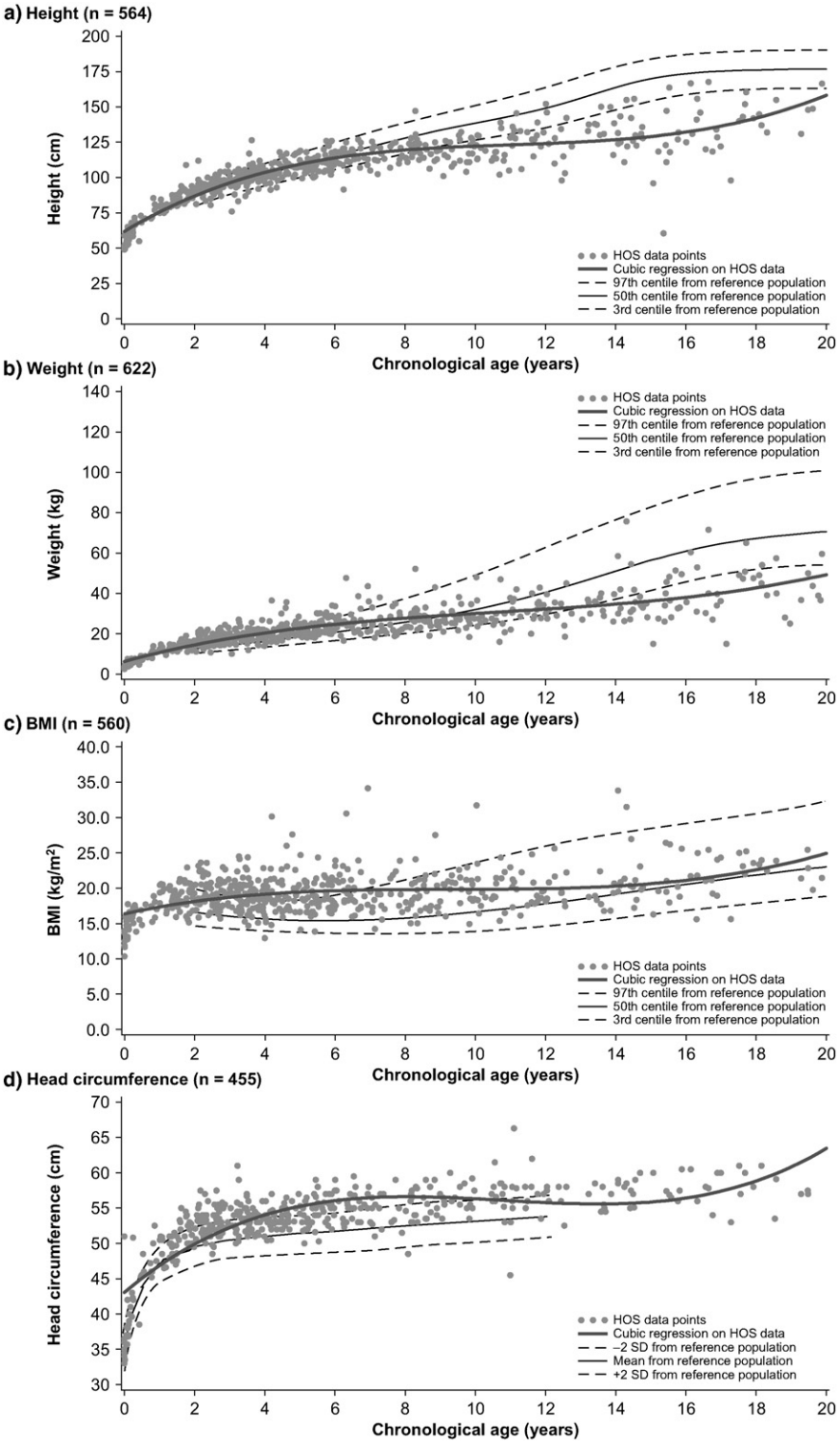

Fig. 1. Descriptive analysis of first measurements of height, weight, BMI and head circumference in untreated patients or before start of ERT in boys with Hunter syndrome. HOS data are presented relative to reference data for boys from the 2000 US Centers for Disease Control Growth Charts [19, 54], except for head circumference, which is plotted relative to Nellhaus reference data [20]. Cubic regression was used to fit the smoothing curve to the HOS data. BMI, body mass index; ERT, enzyme replacement therapy; HOS, Hunter Outcome Survey; SD, standard deviation.

approximately 2.5 years and indicated that boys with Hunter syndrome do not experience a normal pubertal growth spurt, confirming a similar observation in MPS II [13] and in line with reports for other MPSs [22, 23]. Using regression analysis approaches, we have demonstrated for the first time that the presence of cognitive involvement was associated with increased BMI in patients in HOS, and that increased weight and head circumference were more likely to occur in those with cognitive involvement than in those without. However, we did not find an association between the presence of cognitive involvement and impaired linear growth, consistent with results from a previous analysis of HOS data [17]. Our findings are also broadly consistent with the few other published analyses investigating growth-related parameters and disease

Table 2
Median z-score by age group for first measurements of height, weight and BMI in untreated patients or before the start of ERT in boys with Hunter syndrome.

Age group at first measure		z-Score for first measurement		
		Height	Weight	BMI
2–4 years	n	251	271	249
	Median	0.5	1.7	2.0
	Q1; Q3	−0.4; 1.4	0.9; 2.4	1.1; 2.7
>4–8 years	n	143	160	143
	Median	−0.9	0.7	1.6
	Q1; Q3	−1.9; −0.1	−0.1; 1.3	1.0; 2.1
>8–12 years	n	68	75	68
	Median	−3.1	−1.0	1.0
	Q1; Q3	−4.3; −1.7	−1.8; −0.3	0.4; 1.5
>12–16 years	n	36	43	34
	Median	−4.2	−2.8	0.1
	Q1; Q3	−5.0; −2.8	−3.6; −1.4	−0.3, 0.7
>16–20 years	n	28	32	27
	Median	−4.5	−3.7	0.4
	Q1; Q3	−5.8; −3.1	−5.4; −2.0	−0.5, 0.8

BMI, body mass index; ERT, enzyme replacement therapy; Q1, first quartile; Q3, third quartile.

severity in Hunter syndrome, which found short stature and large head circumference in both the severe and attenuated forms of the disease, with slightly earlier onset of short stature in those with the severe form [9, 12].

The underlying causes of growth impairment in Hunter syndrome and the other MPSs are not well understood. It has been hypothesized that GAG storage triggers a complex pathogenic cascade of abnormal biological mechanisms such as disruption of the extracellular matrix [24], alteration of signal transduction pathways, modulation of cytokines and other inflammatory mediators, and alteration of the intracellular targeting pathways, endocytosis, apoptosis and autophagy [25]. In the recent past, many studies on various MPS animal models have shown early abnormalities of chondrocyte organization in the growth plate and architecture of cortical bone [24–30]. These findings may partially help in understanding reasons for growth failure in Hunter syndrome.

Our finding that abnormal linear growth in patients with Hunter syndrome in HOS is independent of cognitive involvement, which might be expected to be associated with more severe and rapidly progressing somatic disease, is in contrast to what is known in many of the other MPSs; for example, rapidly progressing disease is associated with short stature in patients with MPS IV or MPS VI [22, 31]. For clinical purposes, patients with these latter MPSs are therefore often divided into two groups according to whether they exhibit rapid or slow linear growth. An important implication of the findings in our analysis is that this approach of using growth characteristics to predict disease severity may not apply in Hunter syndrome. Disease severity in MPS IV and MPS VI has been reported to correlate with age-adjusted levels of the appropriate urinary GAGs as well as with growth impairment [22, 23, 31–33], but this is also generally considered not to be the case in Hunter syndrome [1, 9, 34]. Taking into consideration that patients with MPS III store only heparan sulfate and have normal linear growth but severe CNS damage [35], whereas patients with MPS VI store only dermatan sulfate and have reduced growth but no CNS damage [22], we may hypothesize that in MPS II dermatan sulfate levels could be related to growth whereas heparan sulfate levels may impact intellectual development. Recently developed tandem mass spectrometry techniques that enable differentiation of dermatan and heparan sulfate will be useful in determining whether levels of these specific GAGs are associated with disease severity (either somatic or neurological) in patients with Hunter syndrome [36–38]. The implications of the various parallels and differences described above for our understanding of the pathophysiology of the MPSs remain to be seen. Of note, it has been reported that joint range of motion (JROM) in patients with Hunter syndrome correlates with height z-score, and that restriction of JROM is more pronounced in those with the severe form of the disease [5]; however, the implication that a height deficit therefore correlates with neurological involvement is not supported by our results. It would be interesting in future to determine the association or otherwise of other somatic manifestations of Hunter syndrome with the presence of cognitive impairment.

The lack of a pubertal growth spurt appears to be a common feature of Hunter syndrome and MPSs I, IV and VI [13, 22, 23, 39]. Normal height gain has been reported to shift from being primarily in the legs during late childhood to being predominantly in the trunk by the second half of puberty [40, 41]. Poor spinal growth has also been identified as the cause of progressive growth failure in young children with MPS-IH following a bone marrow transplant [42]. However a very sophisticated study about various components of growth shows that both leg and trunk growth contribute to the pubertal growth spurt in the normal child [43]. Further studies, including measurement of sitting height as well as full height, are needed to investigate whether spine and legs contribute differently to growth of MPS II patients during puberty, or if both of these components are affected due to impaired response to hormonal stimuli, perhaps resulting from progressive chondrocyte GAG storage and consequent disruption of tissue structure and inflammatory responses. Little is known in general about the characteristics of puberty in Hunter syndrome, for example whether age of onset differs with disease severity. Further analysis using data in HOS was not possible owing to the low number of patients with additional information recorded in the database, limitations associated with how the pubic hair and breast/genital Tanner stage data are captured, and the large number of confounding factors for analyses of variables such as age at first-reported puberty.

We found that patients with Hunter syndrome were heavier than their peers until approximately 9 years of age, and that BMI was high

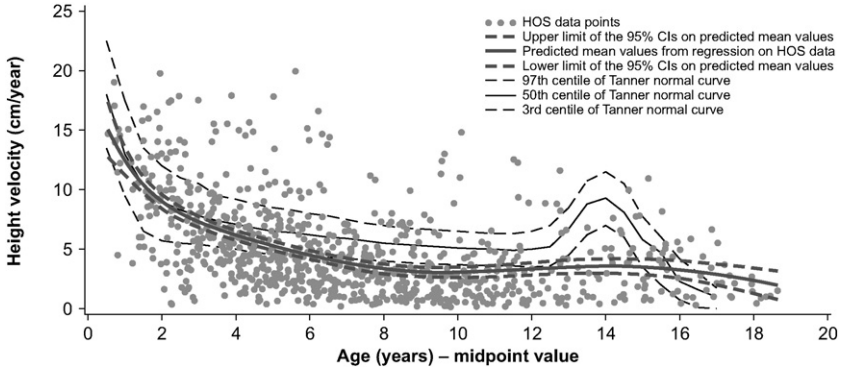

Fig. 2. Analysis of height velocity in untreated patients or before the start of ERT in boys with Hunter syndrome. Height velocity was plotted relative to the Tanner normal curve [21]. Outlying values in the HOS data, defined as those >20 cm/year, were excluded from this analysis of height velocity. Data plotted comprise 865 values from 275 patients. ERT, enzyme replacement therapy.

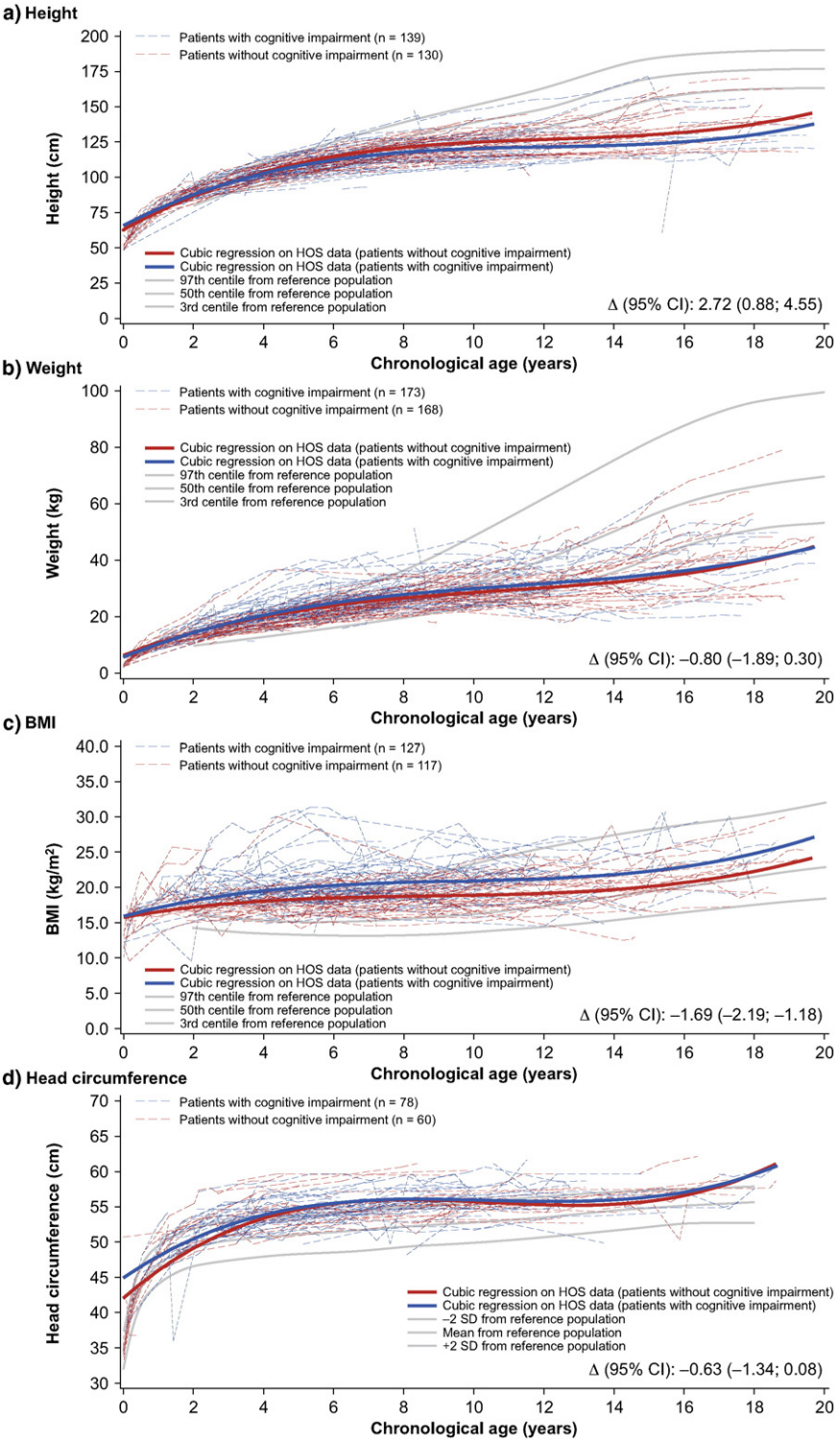

Fig. 3. Regression curves of repeated measurements analysis of the influence of cognitive impairment on height, weight, BMI and head circumference in untreated patients or before the start of ERT in boys with Hunter syndrome. Repeated measurements using linear, quadratic and cubic regression lines to fit growth data over time by age and split by 'Cognitive impairment: yes' versus 'Cognitive impairment: no' using the subset of patients with at least three measurements available. Data are from untreated patients or were collected before the start of ERT. HOS data presented relative to reference data for boys from the 2000 US Centers for Disease Control Growth Charts, except for head circumference, which is plotted relative to Nellhaus reference data. BMI, body mass index; CI, confidence interval; ERT, enzyme replacement therapy; HOS, Hunter Outcome Survey; Δ, difference (patients without cognitive impairment compared with those with cognitive impairment).

until around 14–16 years of age. The reasons for these patterns are not fully understood but low levels of physical activity, coupled with early reduced growth velocity and subsequent reduced height, may play a role. Although our logistic regression modelling found an association between the presence of cognitive involvement and increased weight, the difference was not large and was not apparent in the repeated measurements regression curves. However, both forms of analysis found that cognitive impairment was associated with increased BMI, which was evident from 2 years of age and persisted into adulthood. This finding at such a young age was unexpected, as neither the level of physical

Table 3
Univariate logistic regression analysis of the association between the presence of cognitive impairment and differences in growth parameters compared with reference populations.

Growth parameter	Cohort 1 definition	Cohort 2 definition	Observations used, number of patients (number of events)	OR ('Cognitive impairment: yes' over 'Cognitive impairment: no')[a]	95% CI lower OR	95% CI upper OR	p value
Reduced height	At least one height < 5%	All height > 5%	514 (275)	0.947	0.669	1.339	0.756
Reduced weight	At least one weight < 5%	All weight > 5%	567 (305)	0.665	0.456	0.969	0.034
Increased weight	At least one weight > 95%	All weight < 95%	567 (305)	2.365	1.630	3.433	<0.0001
Increased BMI	At least one BMI > 95%	All BMI < 95%	510 (275)	3.329	2.313	4.791	<0.0001
Increased head circumference	At least one head circumference > 2SDs	All head circumference < 2SDs	441 (231)	1.749	1.195	2.562	0.004

BMI, body mass index; CI, confidence interval; OR, odds ratio; SD, standard deviation.
[a] The odds of having cognitive impairment versus no cognitive impairment for patients with cohort 1 characteristics as opposed to individuals with cohort 2 characteristics.

activity during the first few years of life nor the feeding patterns at this age are expected to differ according to future progression to cognitive impairment. However, hyperorality can be seen from a young age in patients with severe Hunter syndrome (authors' clinical experience) and has also been reported in MPS IIIa [44]. This may be one possible explanation, in conjunction with reduced physical activity and worsening of musculoskeletal functions over time. One further area for consideration is the potential connection between obesity, low-grade inflammation and activation of the innate immune system. GAG accumulation stimulates an inflammatory cascade involving toll-like receptor 4 (TLR4) and tumour necrosis factor-alpha (TNF-α) [30, 45]. The latter has been hypothesized to provide a link between inflammation and obesity [46], and it is possible that this pathway is a factor in the patterns of weight seen in children with Hunter syndrome.

Patients in HOS of all ages had a large head circumference. Whilst our repeated measures analysis found no difference in head circumference with disease severity, logistic regression modelling demonstrated that this characteristic was more frequently observed in those with cognitive impairment than in those without. Large head circumference per se has not previously been associated with CNS involvement in patients with Hunter syndrome [9], and in most cases the pathophysiology is unknown. Although a thickened skull may contribute in some patients, there are likely to be further factors involved. White matter lesions, brain atrophy and hydrocephalus are known to be more common in Hunter syndrome patients with cognitive impairment than without [47–51]. The neurodegenerative course that is often observed in cognitively impaired patients with Hunter syndrome is usually associated with micro- rather than macrocephaly in other diseases; the brain atrophy and loss of brain volume in cognitively impaired patients with Hunter syndrome also suggests that the large head circumference is independent of brain growth. Head growth mostly occurs in the first few years of life [20], which is not only before the defect in linear growth becomes apparent in patients with Hunter syndrome but also when other growth parameters tend to be greater than in reference populations. Whether this reflects commonality in underlying pathophysiology remains to be determined. Finally, hydrocephalus is a well-recognized cause of macrocephaly in the normal population [52], but is, however, thought to account for only a small percentage of cases in Hunter syndrome. Overall, there is no evidence that large head circumference is a clinical predictor of CNS involvement in patients with Hunter syndrome. Further work is required to fully understand the implications of our logistic regression modelling results, for example whether there are sub-groups of patients who have a particularly large head circumference.

It is important to consider the limitations of the current analysis. Patient enrolment and data entry and collection in the HOS registry are at the discretion of participating physicians, and only information collected during routine clinical practice according to the standards of each centre is included. As with any registry, data collection may therefore have certain biases and limitations. For example, height may be measured using different methods at different centres. Nonetheless, calculations of changes in height and growth rate are expected to be accurate due to use of a single method within any given centre [17]. It should also be noted that the accuracy of height measurements may be affected by features of Hunter syndrome such as early-onset musculoskeletal abnormalities (including contractures, joint stiffness and spine and bone deformities) [53] and behavioural difficulties. For this analysis, we used the 'Cognitive impairment: yes/no' question in HOS to divide patients into two groups according to CNS disease severity. This approach has been used previously [17] but we would like to highlight the subjective nature and limitations of this approach, particularly in the context of the broad spectrum and variability of disease in Hunter syndrome [10]. We also considered the possibility that some patients were too young for cognitive impairment to be apparent, but the age breakdown at last cognitive assessment indicated that this was not likely to be a confounding factor (see Appendix A). As the registry grows and our understanding of the disease improves, it may become possible to find other means of achieving this type of analysis from data in HOS.

Despite the inherent limitations described above, there are counterbenefits to registry data. These include the ability to follow a large, mixed-ethnicity population over a long period of time, and that the data reflect real-world clinical practice. As such, data collected in HOS provide an important contribution to our knowledge of the natural history and management of Hunter syndrome.

5. Conclusions

In summary, our findings show that enlarged head circumference, increased weight and increased BMI are more common in patients with MPS II with cognitive impairment than in those without, and confirm that short stature in patients with Hunter syndrome is not associated with cognitive status. In addition, we demonstrated short stature after approximately 8 years of age, large head circumference at all ages and increased body weight and BMI during early childhood. We also found no evidence of a pubertal growth spurt. This description of growth and associated parameters in untreated patients with Hunter syndrome will be a useful basis for future analyses of treatment effects. Importantly, our results indicate that, unlike other MPS disorders, there is no evidence at present that changes in growth characteristics should provide a basis for prediction of disease severity or indicate prognosis in patients with Hunter syndrome.

Role of funding source

Shire sponsors and funds HOS and provides operational and biostatistical support. Medical writing support was provided by Dr Helen Bremner of Oxford PharmaGenesis (Oxford, UK) and was funded by Shire.

Conflicts of interest

RP has received travel grants from Shire, Genzyme (a Sanofi Company), BioMarin and Sobi, research grants from Shire, and honoraria for speaking engagements from Shire, Genzyme (a Sanofi Company) and BioMarin.

SAJ has received honoraria for speaking engagements and assistance with travel to conferences from Shire; he is also engaged in ongoing research projects with Shire, Genzyme (a Sanofi Company), BioMarin, PTC Therapeutics, Inc., Ultragenyx, Synageva BioPharma and Alexion.

PRH has provided consulting support to and received grant support and honoraria for speaking engagements from Shire, BioMarin, Genzyme (a Sanofi Company), PTC Therapeutics, Inc., Alexion/Enobia, Chiesi, ArmaGen, Inventiva Pharma and Fondazione Telethon.

RG has received travel grants from Actelion Pharmaceuticals Ltd, Shire, Genzyme (a Sanofi Company) and BioMarin, research grants from Shire, Actelion Pharmaceuticals Ltd, Amicus Therapeutics, BioMarin, Genzyme (a Sanofi Company) and Synageva, and honoraria for speaking engagements from Actelion Pharmaceuticals Ltd, Shire, Genzyme (a Sanofi Company), BioMarin and Synageva.

NJM has received financial reimbursement for travel expenses from Shire and BioMarin and is also engaged in ongoing research projects with Shire and BioMarin.

Acknowledgments

The authors would like to thank the patients and their families for their participation in HOS, and the HOS Investigators and study staff who contributed data from their patients to the registry. HOS is overseen by scientific advisory boards comprised of physicians experienced in the management of patients with Hunter syndrome. The authors would also like to thank Sylvain Larroque for statistical support and the Pierfranco e Luisa Mariani Foundation, Milano, Italy for its continuous financial support to clinical assistance to metabolic patients (Dr Parini). This publication was supported in part (Dr Harmatz), by the National Center for Advancing Translational Sciences, National Institutes of Health (NIH), through UCSF-CTSI grant number UL1 TR000004. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Appendix A. Age distribution at time of last cognitive category

Table A1 Age distribution of patients in this analysis at time of last cognitive evaluation being recorded in HOS.

N		Overall	'Cognitive impairment: yes'	'Cognitive impairment: no'
		676[a]	322	336
Age at last cognitive evaluation reported in HOS, n (%)	0–2 years	26 (4.0)	4 (1.2)	22 (6.5)
	3–5 years	111 (16.9)	56 (17.4)	55 (16.4)
	6–11 years	218 (33.1)	128 (39.8)	90 (26.8)
	12–17 years	167 (25.4)	96 (29.8)	71 (21.1)
	18–29 years	100 (15.2)	34 (10.6)	66 (19.6)
	≥30 years	36 (5.5)	4 (1.2)	32 (9.5)

HOS, Hunter Outcome Survey.

[a] Information on cognitive impairment was missing for 18 patients; data from these individuals are not included in the table.

References

[1] E.F. Neufeld, J. Muenzer, The mucopolysaccharidoses, in: C.R. Scriver, A.L. Beaudet, W.S. Sly, D. Valle (Eds.), The Metabolic and Molecular Bases of Inherited Disease, McGraw-Hill, New York 2001, pp. 3421–3452.
[2] H.Y. Lin, S.P. Lin, C.K. Chuang, D.M. Niu, M.R. Chen, F.J. Tsai, M.C. Chao, P.C. Chiu, S.J. Lin, L.P. Tsai, W.L. Hwu, J.L. Lin, Incidence of the mucopolysaccharidoses in Taiwan, 1984–2004, Am. J Med Genet A 149A (2009) 960–964.
[3] B.J. Poorthuis, R.A. Wevers, W.J. Kleijer, J.E. Groener, J.G. de Jong, S. van Weely, K.E. Niezen-Koning, O.P. van Diggelen, The frequency of lysosomal storage diseases in The Netherlands, Hum. Genet. 105 (1999) 151–156.
[4] F. Baehner, C. Schmiedeskamp, F. Krummenauer, E. Miebach, M. Bajbouj, C. Whybra, A. Kohlschutter, C. Kampmann, M. Beck, Cumulative incidence rates of the mucopolysaccharidoses in Germany, J. Inherit. Metab. Dis. 28 (2005) 1011–1017.
[5] J. Marucha, A. Jurecka, M. Syczewska, A. Rozdzynska-Swiatkowska, A. Tylki-Szymanska, Restricted joint range of motion in patients with MPS II: correlation with height, age and functional status, Acta Paediatr. 101 (2012) e183–e188.
[6] L.L. Pinto, I.V. Schwartz, A.C. Puga, T.A. Vieira, M.V. Munoz, R. Giugliani, Prospective study of 11 Brazilian patients with mucopolysaccharidosis II, J. Pediatr. 82 (2006) 273–278.
[7] I.D. Young, P.S. Harper, The natural history of the severe form of Hunter's syndrome: a study based on 52 cases, Dev. Med. Child Neurol. 25 (1983) 481–489.
[8] I.D. Young, P.S. Harper, Mild form of Hunter's syndrome: clinical delineation based on 31 cases, Arch. Dis. Child. 57 (1982) 828–836.
[9] I.V. Schwartz, M.G. Ribeiro, J.G. Mota, M.B. Toralles, P. Correia, D. Horovitz, E.S. Santos, I.L. Monlleo, A.C. Fett-Conte, R.P. Sobrinho, D.Y. Norato, A.C. Paula, C.A. Kim, A.R. Duarte, R. Boy, E. Valadares, M. De Michelena, P. Mabe, C.D. Martinhago, J.M. Pina-Neto, F. Kok, S. Leistner-Segal, M.G. Burin, R. Giugliani, A clinical study of 77 patients with mucopolysaccharidosis type II, Acta Paediatr. 96 (2007) 63–70.
[10] S.A. Jones, Z. Almassy, M. Beck, K. Burt, J.T. Clarke, R. Giugliani, C. Hendriksz, T. Kroepfl, L. Lavery, S.P. Lin, G. Malm, U. Ramaswami, R. Tincheva, J.E. Wraith, Mortality and cause of death in mucopolysaccharidosis type II — a historical review based on data from the Hunter Outcome Survey (HOS), J. Inherit. Metab. Dis. 32 (2009) 534–543.
[11] A. Rozdzynska, A. Tylki-Szymanska, A. Jurecka, J. Cieslik, Growth pattern and growth prediction of body height in children with mucopolysaccharidosis type II, Acta Paediatr. 100 (2011) 456–460.
[12] A. Rozdzynska-Swiatkowska, A. Jurecka, J. Cieslik, A. Tylki-Szymanska, Growth patterns in children with mucopolysaccharidosis I and II, World J. Pediatr. (2014).
[13] P. Patel, Y. Suzuki, M. Maeda, E. Yasuda, T. Shimada, K.E. Orii, T. Orii, S. Tomatsu, Growth charts for patients with Hunter syndrome, Mol. Genet. Metab. Rep. 1 (2014) 5–18.
[14] J.E. Wraith, M. Beck, R. Giugliani, J. Clarke, R. Martin, J. Muenzer, Initial report from the Hunter Outcome Survey, Genetics in Medicine 10 (2008) 508–516.
[15] G. Schulze-Frenking, S.A. Jones, J. Roberts, M. Beck, J.E. Wraith, Effects of enzyme replacement therapy on growth in patients with mucopolysaccharidosis type II, J. Inherit. Metab. Dis. 34 (2011) 203–208.
[16] J. Muenzer, M. Beck, R. Giugliani, Y. Suzuki, A. Tylki-Szymanska, V. Valayannopoulos, A. Vellodi, J.E. Wraith, Idursulfase treatment of Hunter syndrome in children younger than 6 years: results from the Hunter Outcome Survey, Genetics in Medicine 13 (2011) 102–109.
[17] S.A. Jones, R. Parini, P. Harmatz, R. Giugliani, J. Fang, N.J. Mendelsohn, The effect of idursulfase on growth in patients with Hunter syndrome: data from the Hunter Outcome Survey (HOS), Mol. Genet. Metab. 109 (2013) 41–48.
[18] T. Khosla, C.R. Lowe, Indices of obesity derived from body weight and height, Br. J. Prev. Soc. Med. 21 (1967) 122–128.
[19] R.J. Kuczmarski, C.L. Ogden, L.M. Grummer-Strawn, K.M. Flegal, S.S. Guo, R. Wei, Z. Mei, L.R. Curtin, A.F. Roche, C.L. Johnson, CDC growth charts: United States, Adv. Data (2000) 1–27.
[20] G. Nellhaus, Head circumference from birth to eighteen years. Practical composite international and interracial graphs, Pediatrics 41 (1968) 106–114.
[21] J.M. Tanner, R.H. Whitehouse, Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty, Arch. Dis. Child. 51 (1976) 170–179.
[22] A. Quartel, C.J. Hendriksz, R. Parini, S. Graham, P. Lin, P. Harmatz, Growth charts for individuals with mucopolysaccharidosis VI (Maroteaux–Lamy Syndrome), JIMD Rep. 18 (2015) 1–11.
[23] P. Harmatz, K.E. Mengel, R. Giugliani, V. Valayannopoulos, S.P. Lin, R. Parini, N. Guffon, B.K. Burton, C.J. Hendriksz, J. Mitchell, A. Martins, S. Jones, N. Guelbert, A. Vellodi, C. Hollak, P. Slasor, C. Decker, The Morquio A Clinical Assessment Program: baseline results illustrating progressive, multisystemic clinical impairments in Morquio A subjects, Mol. Genet. Metab. 109 (2013) 54–61.
[24] J.M. Heppner, F. Zaucke, L.A. Clarke, Extracellular matrix disruption is an early event in the pathogenesis of skeletal disease in mucopolysaccharidosis I, Mol. Genet. Metab. 114 (2015) 146–155.
[25] L.A. Clarke, Pathogenesis of skeletal and connective tissue involvement in the mucopolysaccharidoses: glycosaminoglycan storage is merely the instigator Rheumatology (Oxford) 50 Suppl 5 (2011) v13–18.
[26] J.D. Nuttall, L.K. Brumfield, N.L. Fazzalari, J.J. Hopwood, S. Byers, Histomorphometric analysis of the tibial growth plate in a feline model of mucopolysaccharidosis type VI, Calcif. Tissue Int. 65 (1999) 47–52.
[27] S. Wilson, S. Hashamiyan, L. Clarke, P. Saftig, J. Mort, V.M. Dejica, D. Bromme, Glycosaminoglycan-mediated loss of cathepsin K collagenolytic activity in MPS I contributes to osteoclast and growth plate abnormalities, Am. J. Pathol. 175 (2009) 2053–2062.

[28] J.A. Metcalf, Y. Zhang, M.J. Hilton, F. Long, K.P. Ponder, Mechanism of shortened bones in mucopolysaccharidosis VII, Mol. Genet. Metab. 97 (2009) 202–211.
[29] L.J. Smith, G. Baldo, S. Wu, Y. Liu, M.P. Whyte, R. Giugliani, D.M. Elliott, M.E. Haskins, K.P. Ponder, Pathogenesis of lumbar spine disease in mucopolysaccharidosis VII, Mol. Genet. Metab. 107 (2012) 153–160.
[30] C.M. Simonaro, M. D'Angelo, X. He, E. Eliyahu, N. Shtraizent, M.E. Haskins, E.H. Schuchman, Mechanism of glycosaminoglycan-mediated bone and joint disease: implications for the mucopolysaccharidoses and other connective tissue diseases, Am. J. Pathol. 172 (2008) 112–122.
[31] C.J. Hendriksz, P. Harmatz, M. Beck, S. Jones, T. Wood, R. Lachman, C.G. Gravance, T. Orii, S. Tomatsu, Review of clinical presentation and diagnosis of mucopolysaccharidosis IVA, Mol. Genet. Metab. 110 (2013) 54–64.
[32] S.J. Swiedler, M. Beck, M. Bajbouj, R. Giugliani, I. Schwartz, P. Harmatz, J.E. Wraith, J. Roberts, D. Ketteridge, J.J. Hopwood, N. Guffon, M.C. Sa Miranda, E.L. Teles, K.·I. Berger, C. Piscia-Nichols, Threshold effect of urinary glycosaminoglycans and the walk test as indicators of disease progression in a survey of subjects with Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome), Am. J. Med. Genet. A 134A (2005) 144–150.
[33] V·.C. Dung, S. Tomatsu, A.M. Montano, G. Gottesman, M.B. Bober, W. Mackenzie, M. Maeda, G.A. Mitchell, Y. Suzuki, T. Orii, Mucopolysaccharidosis IVA: correlation between genotype, phenotype and keratan sulfate levels, Mol. Genet. Metab. 110 (2013) 129–138.
[34] M. Scarpa, Z. Almassy, M. Beck, O. Bodamer, I.A. Bruce, L. De Meirleir, N. Guffon, E. Guillen-Navarro, P. Hensman, S. Jones, W. Kamin, C. Kampmann, C. Lampe, C.A. Lavery, E.L. Teles, B. Link, A.M. Lund, G. Malm, S. Pitz, M. Rothera, C. Stewart, A. Tylki-Szymanska, A. van der Ploeg, R. Walker, J. Zeman, J.E. Wraith, Mucopolysaccharidosis type II: European recommendations for the diagnosis and multidisciplinary management of a rare disease, Orphanet. J. Rare. Dis. 6 (2011) 72.
[35] J. de Ruijter, L. Broere, M.F. Mulder, A.T. van der Ploeg, M.E. Rubio-Gozalbo, S.B. Wortmann, G. Visser, F.A. Wijburg, Growth in patients with mucopolysaccharidosis type III (Sanfilippo disease), J. Inherit. Metab. Dis. 37 (2014) 447–454.
[36] H. Zhang, T. Wood, S.P. Young, D.S. Millington, A straightforward, quantitative ultra-performance liquid chromatography–tandem mass spectrometric method for heparan sulfate, dermatan sulfate and chondroitin sulfate in urine: an improved clinical screening test for the mucopolysaccharidoses, Mol. Genet. Metab. 114 (2015) 123–128.
[37] C.K. Chuang, H.Y. Lin, T.J. Wang, C.C. Tsai, H.L. Liu, S.P. Lin, A modified liquid chromatography/tandem mass spectrometry method for predominant disaccharide units of urinary glycosaminoglycans in patients with mucopolysaccharidoses, Orphanet. J. Rare. Dis. 9 (2014) 135.
[38] H. Osago, T. Shibata, N. Hara, S. Kuwata, M. Kono, Y. Uchio, M. Tsuchiya, Quantitative analysis of glycosaminoglycans, chondroitin/dermatan sulfate, hyaluronic acid, heparan sulfate, and keratan sulfate by liquid chromatography–electrospray ionization-tandem mass spectrometry, Anal. Biochem. 467 (2014) 62–74.
[39] C.J. Gardner, N. Robinson, T. Meadows, R. Wynn, A. Will, J. Mercer, H.J. Church, K. Tylee, J.E. Wraith, P.E. Clayton, Growth, final height and endocrine sequelae in a UK population of patients with Hurler syndrome (MPS1H), J. Inherit. Metab. Dis. 34 (2011) 489–497.
[40] J.M. Tanner, Foetus Into Man. Physical Growth From Conception to Maturity, Castlemead Publications, 1989.
[41] A. Dimeglio, Growth in pediatric orthopaedics, J. Pediatr. Orthop. 21 (2001) 549–555.
[42] A. Vellodi, E.P. Young, A. Cooper, J.E. Wraith, B. Winchester, C. Meaney, U. Ramaswami, A. Will, Bone marrow transplantation for mucopolysaccharidosis type I: experience of two British centres, Arch. Dis. Child. 76 (1997) 92–99.
[43] J. Karlberg, On the construction of the infancy–childhood–puberty growth standard, Acta Paediatr. Scand. Suppl 356 (1989) 26–37.
[44] M. Potegal, B. Yund, K. Rudser, A. Ahmed, K. Delaney, I. Nestrasil, C.B. Whitley, E.G. Shapiro, Mucopolysaccharidosis type IIIA presents as a variant of Kluver–Bucy syndrome, J. Clin. Exp. Neuropsychol. 35 (2013) 608–616.
[45] C.M. Simonaro, Cartilage and chondrocyte pathology in the mucopolysaccharidoses: the role of glycosaminoglycan-mediated inflammation, J. Pediatr. Rehabil. Med. 3 (2010) 85–88.
[46] J.P. Bastard, M. Maachi, C. Lagathu, M.J. Kim, M. Caron, H. Vidal, J. Capeau, B. Feve, Recent advances in the relationship between obesity, inflammation, and insulin resistance, Eur. Cytokine Netw. 17 (2006) 4–12.
[47] O. Gabrielli, G. Polonara, L. Regnicolo, V. Petroni, T. Scarabino, G.V. Coppa, U. Salvolini, Correlation between cerebral MRI abnormalities and mental retardation in patients with mucopolysaccharidoses, Am. J. Med. Genet. A 125A (2004) 224–231.
[48] L. Vedolin, I.V. Schwartz, M. Komlos, A. Schuch, A.C. Puga, L.L. Pinto, A.P. Pires, R. Giugliani, Correlation of MR imaging and MR spectroscopy findings with cognitive impairment in mucopolysaccharidosis II, AJNR Am. J. Neuroradiol. 28 (2007) 1029–1033.
[49] Z. Fan, M. Styner, J. Muenzer, M. Poe, M. Escolar, Correlation of automated volumetric analysis of brain MR imaging with cognitive impairment in a natural history study of mucopolysaccharidosis II, AJNR Am. J. Neuroradiol. 31 (2010) 1319–1323.
[50] J.B. Holt, M.D. Poe, M.L. Escolar, Natural progression of neurological disease in mucopolysaccharidosis type II, Pediatrics 127 (2011) e1258–e1265.
[51] R. Parini, M. Rigoldi, L. Tedesco, L. Boffi, A. Brambilla, S. Bertoletti, A. Boncimino, A. Del Longo, P. De Lorenzo, R. Gaini, D. Gallone, S. Gasperini, C. Giussani, M. Grimaldi, D. Grioni, P. Meregalli, G. Messinesi, F. Nichelli, M. Romagnoli, P. Russo, E. Sganzerla, G. Valsecchi, A. Biondi, Enzymatic replacement therapy for Hunter disease: up to 9 years experience with 17 patients, Mol. Genet. Metab. Rep. 3 (2015) 65–74.
[52] C.A. Williams, A. Dagli, A. Battaglia, Genetic disorders associated with macrocephaly, Am. J. Med. Genet. A 146A (2008) 2023–2037.
[53] B. Link, L.L. de Camargo Pinto, R. Giugliani, J.E. Wraith, N. Guffon, E. Eich, M. Beck, Orthopedic manifestations in patients with mucopolysaccharidosis type II (Hunter syndrome) enrolled in the Hunter Outcome Survey, Orthop. Rev. (Pavia) 2 (2010) e16.
[54] J.M. Tanner, P.S. Davies, Clinical longitudinal standards for height and height velocity for North American children, J. Pediatr. 107 (1985) 317–329.