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

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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].

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[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.

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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