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Short Communication

Birth weight in patients with mucopolysaccharidosis type II: Data from the Hunter Outcome Survey (HOS)

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ABSTRACT

There is a need to identify early disease markers to facilitate diagnosis of mucopolysaccharidosis type II (MPS II; Hunter syndrome). Mean birth weight and its association with disease severity was investigated in 609 patients enrolled in the Hunter Outcome Survey (HOS). This analysis indicated that birth weight is not an early marker of MPS II and is not associated with disease severity. It remains important to investigate the utility of other factors for early/pre-symptomatic diagnosis.

1. Introduction

Mucopolysaccharidosis type II (MPS II; Hunter syndrome; OMIM# 30990) is a rare, progressive, X-linked disorder caused by deficiency of the lysosomal enzyme iduronate-2-sulfatase (EC 3.1.6.13) [1]. The severity of MPS II spans a broad range; although all patients experience somatic disease manifestations, about two-thirds of patients display progressive central nervous system (CNS) involvement, which is absent in the remaining patients [1,2]. The variable clinical presentation of MPS II, non-specific signs and symptoms that are similar to common childhood ailments, and a lack of disease awareness, means that diagnosis is challenging and frequently delayed [3]. Specific treatment is available in the form of weekly enzyme replacement therapy (ERT) with intravenous idursulfase (Elaprase®, Shire, Lexington, MA, USA). Since timely diagnosis and treatment initiation may improve patient outcomes, the identification of early disease markers is critical, especially those that could indicate a need for screening at birth [3].

Previous studies have analysed birth parameters in patients with MPS II, and mean birth weight has been reported to be slightly higher in patients with cognitive impairment than in those without [2,4–8]. However, many of these studies were conducted in small, restricted patient populations and data on the correlation of birth weight with disease severity are limited. Data available in the Hunter Outcome Survey (HOS) were used to investigate whether birth weight differs in newborns with MPS II when compared with population-based reference values, and whether there is an association with disease severity.

2. Materials and methods

2.1. Patient population

HOS is a large, multicenter, longitudinal, observational registry of patients with MPS II that collects data on the natural history of the disease and the long-term safety and effectiveness of ERT with idursulfase. Before enrolment, Independent Review Board/Ethics Committee approval was obtained for all participating centers, and each patient, their parents or a legal representative provided written informed consent. For those patients who were deceased prior to HOS entry, consent was obtained from patients' families. All patient information in the registry is managed in accordance with national data protection standards. Patients followed prospectively (alive at HOS entry) and retrospectively (died before enrolment) were included in this analysis. Brothers with the same date and place of birth but who were not formally recorded in the database as twins, were excluded (as twins

Abbreviations: ERT, enzyme replacement therapy; HOS, Hunter Outcome Survey; MPS II, mucopolysaccharidosis type II; SD, standard deviation

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Table 1
Birth weight in patients in this analysis (N = 609) and the relationship between birth weight and subsequent development of cognitive impairment.

Parameter	Overall (N = 609)	Patients with cognitive impairment status available (N = 578)		p value[a]
		Cognitive impairment (N = 341)	No cognitive impairment (N = 237)	
Birth weight (all patients), g				
Mean (SD)	3420.0 (621.5)	3426.2 (609.9)	3430.8 (620.9)	0.928
Median (10th, 90th percentiles)	3447.0[b] (2750.0, 4091.0)	3430.0 (2750.0, 4091.0)	3492.0 (2750.0, 4091.0)	
z-Score[c]				
Mean (SD)	− 0.03 (1.28)	− 0.02 (1.19)	0.00 (1.42)	0.818
Median (10th, 90th percentiles)	− 0.04 (− 1.54, 1.36)	− 0.04 (− 1.54, 1.44)	0.00 (− 1.52, 1.44)	
Birth weight for gestational age category, n (%)[d]				
Low (< 3rd percentile)	38 (6.2)	21 (58.3)	15 (41.7)	N/A
Appropriate (≥ 3rd ≤ 97th percentile)	542 (88.9)	306 (59.5)	208 (40.5)	
High (> 97th percentile)	29 (4.8)	14 (50.0)	14 (50.0)	

N/A, non-applicable; SD, standard deviation.
[a] Cognitive impairment 'Yes' and cognitive impairment 'No' groups were compared using a Student's *t*-test.
[b] This value corresponds to the 58th percentile for boys (World Health Organization child growth standards) [18].
[c] Birth weight for gestational age z-score calculated according to population-based reference values [10].
[d] Percentiles calculated according to population-based reference values [10].

tend to have a lower birth weight than singletons) [9]. Patients with a positive family history of MPS II or those for whom information on family history of MPS II was missing were excluded from the analysis of age at diagnosis.

2.2. Data analysis

HOS is designed to collect data on individuals diagnosed with MPS II that has been obtained during routine patient visits and assessments [2]. Data from patients who died before enrolment (retrospective patients) may also be entered in the database. Birth weight for gestational age z-scores (the number of standard deviations from the reference mean) were calculated based on population-based reference values [10]. To gauge the validity of the chosen reference population, a comparison of mean birth weight in the overall analysis population (n = 609) with that in a subgroup of the analysis population who were of Caucasian origin (n = 463) was performed. Low birth weight for gestational age was defined as < 3rd percentile and high birth weight for gestational age as > 97th percentile, based on population-based reference values [10].

Disease severity was established on the basis of the presence or absence of cognitive impairment at any time from birth to the last visit recorded in HOS, based on the answer to the question 'Cognitive impairment? Yes/No'. A Student's *t*-test was used to assess the significance of differences in birth weight between patients with and without cognitive involvement.

3. Results

As of January 2015, data on birth weight and gestational age were available for 609 patients with MPS II who were enrolled in HOS. Of these individuals, 516 were alive at HOS entry (prospective patients) and 93 were deceased before enrolment (retrospective patients). A total of 463 patients were of Caucasian origin (Table 1 and Supplementary Table 1). As mean (standard deviation [SD]) birth weight in the Caucasian sub-population was similar to that in the overall analysis population (3430.2 [627.0] g and 3420.0 [621.5] g, respectively), reference values from Kramer et al. [10] were used for the calculation of birth weight for gestational age z-scores.

The mean birth weight for gestational age in patients with MPS II was similar to that in the reference population, as demonstrated by a mean [SD] birth weight for gestational age z-score of − 0.03 [1.28] (Table 1). The distribution of patients by birth weight for gestational age z-score is shown in Supplementary Fig. 1. Approximately 6% of patients (38/609) were considered to have a low birth weight for gestational age, while almost 5% (29/609) had a high birth weight for gestational age (Table 1). There was no apparent association between birth weight and the presence or absence of cognitive impairment (Table 1).

4. Discussion

Using data from over 600 individuals with MPS II, we found that the mean birth weight of these patients is similar to that of the general population. Our results from a large and diverse population of patients confirm the findings of previous smaller-scale studies, which have not reported statistically significant differences between the birth weights of patients with MPS II and the general population [4,5,8]. In addition, we found that birth weight was not associated with disease severity as measured by the presence or absence of cognitive impairment. This is an important finding, as anecdotal evidence and findings from other studies have suggested that patients with cognitive impairment may have higher birth weights than those without [4,6]. This is also consistent with the lack of correlation between CNS involvement and height, weight and head circumferences reported in older patients [11,12].

As with any study using registry data, this analysis has several potential limitations. Patient enrolment, data entry, and data collection are at the discretion of participating physicians and there may be regional variation in the methods used for obtaining clinical measurements. In addition, other causes of high birth weight, such as maternal diabetes, are not recorded in the database and so cannot be excluded. It is also important to note that the assessment of cognitive impairment recorded in HOS is not necessarily based on the results of standardized cognitive tests but may instead be based on a brief, subjective, clinical impression. In addition, the variable clinical presentation and rate of progression of MPS II means that although some patients may display little or no neurological involvement, they may be considered to have severe disease on the basis of their somatic disease signs and symptoms. Finally, as HOS only collects data from patients with MPS II we compared birth weights with those from a Canadian reference population, and so country-specific variation in birth weight is not accounted for.

The accumulation of urinary glycosaminoglycans is thought to begin prenatally [13,14], and so it is important that individuals with MPS II are diagnosed and receive care as early as possible [15–17]. However, the early identification of patients with the disease is challenging, particularly in the absence of a positive family history of the disease. This analysis indicates that birth weight is not a suitable marker to facilitate newborn screening for MPS II. Thus, there remains a

need to investigate whether other factors or auxological data, such as head circumference and body length at birth, may be indicators that could be used to aid earlier, pre-symptomatic diagnosis.

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Conflicts of interest

Olaf Bodamer: Dr. Bodamer has received research grants and honoraria from Genzyme (a Sanofi company) and Shire, and honoraria from PTC.

Maurizio Scarpa: Dr. Scarpa has received grants, travel support and honoraria from BioMarin, Genzyme (a Sanofi company) and Shire.

Christina Hung: Dr. Hung has no conflicts of interest.

Tom Pulles: Dr. Pulles is a full-time employee of Ultragenyx Pharmaceutical, Inc., and was previously a full-time employee and shareholder of Shire.

Roberto Giugliani: Professor Giugliani has received travel grants from BioMarin, Genzyme (a Sanofi company) and Shire, research grants from Actelion Pharmaceuticals, BioMarin, Genzyme (a Sanofi company), Shire and Synageva BioPharma, and honoraria for speaking engagements from BioMarin, Genzyme (a Sanofi company), Shire and Synageva BioPharma.

Contributors' statements

Olaf Bodamer: Dr. Bodamer made a substantial contribution to the conception and design of the analysis and interpretation of data, drafted the initial manuscript and revised it critically for important intellectual content, approved the final manuscript as submitted and agrees to be accountable for all aspects of the work.

Maurizio Scarpa: Dr. Scarpa made a substantial contribution to the conception and design of the analysis and interpretation of data, was involved with developing the draft of the article and revising it critically for important intellectual content, approved the final manuscript as submitted and agrees to be accountable for all aspects of the work.

Christina Hung: Dr. Hung made a substantial contribution to the conception and design of the analysis and interpretation of data, was involved with developing the draft of the article and revising it critically for important intellectual content, approved the final manuscript as submitted and agrees to be accountable for all aspects of the work.

Tom Pulles: Dr. Pulles made a substantial contribution to the conception and design of the analysis and interpretation of data, was involved with developing the draft of the article and revising it critically for important intellectual content, approved the final manuscript as submitted and agrees to be accountable for all aspects of the work.

Roberto Giugliani: Professor Giugliani made a substantial contribution to the conception and design of the analysis and interpretation of data, was involved with developing the draft of the article and revising it critically for important intellectual content, approved the final manuscript as submitted and agrees to be accountable for all aspects of the work.

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