Molecular Genetics and Metabolism 99 (2010) 10–17

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

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

Anthropometric data of 14 patients with mucopolysaccharidosis I: Retrospective analysis and efficacy of recombinant human α-L-iduronidase (laronidase)

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ARTICLE INFO

Article history:
Received 24 August 2009
Accepted 24 August 2009
Available online 27 August 2009

Keywords:
Anthropometric features
Growth patterns
Growth retardation
Enzyme replacement therapy
Mucopolysaccharidosis type I
Hurler syndrome
Hurler–Scheie syndrome
Scheie syndrome

ABSTRACT

Objectives: Our goal was to evaluate growth patterns in terms of body height, weight, head and chest circumference in patients with mucopolysaccharidosis type I (MPS I) without treatment and after enzyme replacement therapy (ERT) with α-L-iduronidase (laronidase). *Patients and methods:* Anthropometric features of 14 patients with MPS I were followed from birth until the introduction of ERT (group 1–1st year of life, group 2 ⩾3rd year of life), after 52–260 weeks of ERT and periodically during treatment. The data since birth until beginning of treatment was obtained by retrospective review of patients' charts. Patients received intravenous laronidase at 100 U/kg (0.58 mg/kg) weekly for 52–260 weeks. *Results:* Patients from group 1 ($n = 7$) and group 2 ($n = 7$) had similar characteristics at the time of birth but showed significant difference when compared with healthy population. Growth patterns were associated significantly with the MPS I at birth. After 96–260 weeks of ERT, patients receiving laronidase (group 1) compared with group 2 did not show statistically significant improvement. *Conclusions:* Anthropometric features of patients with MPS I significantly differ from the healthy population. Children with MPS I grew considerably slower, and differences between healthy and affected children increased with age. In studied patients with MPS I, laronidase did not appear to alter the growth patterns.

Introduction

The mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders attributable to defective catabolism of glycosaminoglycans (GAGs), leading to severe joint and bone disease [1]. As glycosaminoglycans accumulate within the lysosomes, progressive organ dysfunction and widespread tissue damage results [1]. Mucopolysaccharidosis type I (MPS I) is caused by the deficiency of the enzyme α-L-iduronidase (IDUA; EC 3.2.1.76) [1]. MPS I has a wide spectrum of clinical severity and three different clinical phenotypes have been described, each representing different degrees of disease severity within a continuous spectrum: Hurler syndrome (severe, OMIM 607016), Hurler–Scheie syndrome (intermediate, OMIM 607015), and Scheie syndrome (attenuated, OMIM 607016) [1–3].

MPS I leads to profound disruption in the normal mechanism of growth and development. A major feature of this disorder is abnormal bone and cartilage development leading to anterior hypoplasia of lumbar vertebrae, enlarged diaphyses of long bones, underdeveloped epiphyseal centers, marked dwarfism and degenerative joint disease [1]. These abnormalities arise from a lack of skeletal remodelling, disordered endochondral and intramembranous ossification, disruption of normal elastogenesis and the infiltration by GAGs [4,5]. It has been shown that inflammation, secondary to GAG accumulation, is a critical aspect of MPS disorder and contributes to the bone disease [6].

Currently, both hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT) using laronidase (recombinant human α-L-iduronidase, Aldurazyme) are available for MPS I. ERT has been shown to be effective in ameliorating some of the clinical manifestation of MPS disease. Among positive effects are decreased hepatosplenomegaly, improved respiratory function and physical capacity [2,7]. However, long-term effect of ERT on the natural history of growth patterns is less clear and there are no studies dealing exclusively with detailed anthropometric features after treatment with ERT. Moreover, in none of the previous studies adequate anthropometric measuring techniques were applied and performed by the same anthropology specialist.

Abbreviations: ERT, enzyme replacement therapy; GAG, glycosaminoglycan; HSCT, hematopoietic stem cell transplantation; MPS I, mucopolysaccharidosis type I; SD, standard deviation.

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doi:10.1016/j.ymgme.2009.08.008

The objective of this study was to analyze the general growth patterns (body height, weight, head and chest circumference) in 14 patients with MPS I with respect to standards from a general population and to assess differences in anthropometric features both retrospectively since birth until introduction of ERT as well as after 52–260 weeks of treatment with laronidase (Aldurazyme).

Materials and methods

Study design

The study objectives were as follows:

- To evaluate growth patterns in terms of body height, weight, head and chest circumference in patients with MPS I without treatment since birth until introduction of ERT.
- To evaluate the effectiveness of laronidase (Aldurazyme, BioMarin Pharmaceutical Inc., Novato, Calif and Genzyme Corporation, Cambridge, Mass) on anthropometric features such as height, weight, head and chest circumference in patients with MPS I.

All patients were enrolled at The Children's Memorial Health Institute (CMHI) in Poland. They traveled to CMHI for the two first infusions of laronidase as well as for a comprehensive periodic biochemical and clinical evaluation. The following laronidase infusions took place in regional hospitals.

To achieve the first aim of the study each patient's clinical records were reviewed retrospectively.

Patients

All patients enrolled in the study were naive to laronidase therapy and had to have a diagnosis of MPS I confirmed by the biochemical determination of α-L-iduronidase deficiency in leukocytes and by molecular analysis.

The demographic characteristics of the 14 MPS I patients are listed in Table 1.

Prior to entering the initial study, all patients exhibited a range of clinical problems reflecting the multi-systemic and progressive nature of MPS I. The spectrum of symptoms included hepatosplenomegaly, recurrent inguinal/umbilical hernias, dysostosis multiplex, joint stiffness, flexion contractures, airway obstruction, cardiac valve disease, corneal clouding, hearing deficit, frequent infections, mental retardation. All patients have been investigated for the presence of hydrocephalus, which was present in two of them and required shunts.

In all patients younger than 2 years, HSCT was considered, but refused by majority patients' parents (16 out of 17) and therefore these patients received ERT. Only patient 1 received HSCT after 52 weeks of ERT. The patient died soon after HSCT due to post-engraftment complication.

All patients were divided in two following groups depending on the age of introduction of ERT.

Group 1: The first group consisted of 7 patients who were 1 year old at the time of introduction of ERT.

Group 2: The second group consisted of 7 patients who were at least 3 years of age at the time of introduction of ERT.

Three years were chosen as a cut-off between groups, because patients in group 2 were born before ERT became available and therefore they received the treatment at a later age.

Ethical consideration

The protocol was approved by the human-subjects institutional review board at The Children's Memorial Health Institute. Written informed consent had to be provided by the parents or legal guardians. The study was designed and conducted in compliance with the principles of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for Good Clinical Practice.

Laronidase treatment

All patients received weekly intravenous infusions of 100 U/kg (0.58 mg/kg) laronidase (Aldurazyme, BioMarin Pharmaceutical Inc., Novato, Calif and Genzyme Corporation, Cambridge, Mass).

Evaluation of efficacy

The primary efficacy endpoint variables were anthropometric features body height, weight, head and chest circumference. These efficacy measures were taken once at baseline, after 52–260 weeks of treatment and periodically during treatment (at weeks 24, 48, 72, 96 weeks and annually after the 96th week). Until the age of 3 years length was measured in the supine position using a liberometer (accuracy to 1 mm). The same measurements of the older children were performed as standing height using a stadiometer (accuracy to 1 mm). Weight was measured using an electronic scale accurate within 0.05 kg. A non-stretchable tape was used to assess head and chest circumference (accuracy to 5 mm). All assessments were performed by the same anthropologist.

Biochemical studies included measurement of urinary glycosaminoglycan excretion. Urinary GAG excretion was measured in

Table 1
Patient characteristics (demographic, molecular characteristics and clinical phenotypes).

Patient No.	Age (y) Diagnosis	Age (y) Baseline	Age (y) Current	Total laronidase exposure (week)	Gender	Mutations	Phenotype
Group 1							
01	5/12	1	2	52	M	Q70X/Q70X	Hurler
02	10/12	1	4	156	M	W402X/W402X	Hurler
03	1	1	5	208	M	Q70X/Q70X	Hurler
04	8/12	1	5	208	M	Δ349/Δ349	Hurler
05	1	1	5	208	M	Q70X/W402X	Hurler
06	8/12	1	2	52	F	Q70X/W402X	Hurler
07	8/12	1	2	52	M	Q70X/Q70X	Hurler
Group 2							
08	1.5	7	11	208	M	Q70X/Q70X	Hurler
09	7	10	14	208	F	W402X/IVS11 + 5G > A	Hurler
10	4	5	9	208	F	Q70X/Δ349	Hurler/Scheie
11	2	3	6	156	M	Q70X/Y76C/H449 N	Scheie
12	5	15	19	208	M	Q70X/G265R	Scheie
13	3	15	19	208	M	134del112/X645R	Scheie
14	1.8	5.5	7.5	104	M	Q70X/134del112	Hurler