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Cognitive and neuroradiological improvement in three patients with attenuated MPS I treated by laronidase ☆

V. Valayannopoulos [a,*], N. Boddaert [b], V. Barbier [a], M. Le Merrer [c], C. Caillaud [d], P. de Lonlay [a]

[a] Reference Center for Inherited Metabolic Disorders, Assistance Publique-Hôpitaux de Paris, Necker-Enfants Malades Hospital, University Paris Descartes, Paris, France
[b] Pediatric Radiology, Assistance Publique-Hôpitaux de Paris, Necker-Enfants Malades Hospital, University Paris Descartes, Paris, France
[c] Genetics Department, Assistance Publique-Hôpitaux de Paris, Necker-Enfants Malades Hospital, University Paris Descartes, Paris, France
[d] Genetic Biochemistry Laboratory, Cochin Hospital, University Paris Descartes, Paris, France

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ABSTRACT

Stem cell transplantation is not appropriate first-line treatment for attenuated phenotypes of mucopolysaccharidosis type I (MPS I). In three patients with attenuated MPSA I treated by laronidase, Patients 2 and 3 displayed significant cognitive improvement within 2 years; Patients 1 and 3 displayed improvement on MRI scans of the brain.

Mucopolysaccharidosis type I (MPS I) is a progressive, multisystemic lysosomal storage disease caused by a profound loss of α-L-iduronidase activity that leads to accumulation of glycosaminoglycans, especially heparan and dermatan sulfate, in virtually all body tissues. MPS I has a spectrum of phenotypes, which are currently divided arbitrarily into three groups: Hurler, Hurler–Scheie and Scheie syndromes. Age of onset, rapidity of disease progression, and involvement of the central nervous system vary from the most severe (Hurler syndrome), with onset in infancy and eventual loss of cognition, to more attenuated phenotypes (Hurler–Scheie syndrome and Scheie syndrome) in which onset occurs later in childhood and there is only moderate or no central nervous system involvement. The main difference between the two attenuated phenotypes is more pronounced osteoarticular and visceral involvement in Hurler–Scheie syndrome.

Hemopoietic stem cell transplantation (HSCT) before 2 years of age is the recommended treatment for patients with severe MPS I [1–4], but due to the associated risks (15% mortality) [1], it is not the first option for patients with attenuated MPS I. Enzyme replacement therapy (ERT) with laronidase, which has been available since 2003 for treatment of the non-neurocognitive aspects of MPS I, has been shown to improve respiratory function, endurance, mobility and range of motion, organomegaly, left ventricular hypertrophy, urinary glycosaminoglycan excretion, and quality of life [5–9]. Because laronidase does not cross the blood–brain barrier, it is not expected to exert any effect on the central nervous system.

We describe cognitive outcomes and brain magnetic resonance imaging (MRI) changes in three patients with attenuated MPS I following 3.5–4.5 years of treatment with laronidase, based on retrospective examination of routine clinical assessments.

Methods

Patients

Patients 1, 2 (females) and 3 (male) were unrelated and were diagnosed with MPS I at ages 10, 6 and 3.5 years, respectively. The patients each had mild or no cognitive impairment and only mild visceral symptoms, and were considered to have attenuated forms

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* Corresponding author. Address: Reference Center for Metabolic Disorders, Hôpital Necker-Enfants Malades, 149, rue des Sèvres, 75015 Paris, France.
E-mail address: vassili.valaya@nck.aphp.fr (V. Valayannopoulos).

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of MPS I: Scheie syndrome in Patients 1 and 2 and Hurler–Scheie syndrome in Patient 3 because of marked osteoarticular involvement. Patient 1 had normal cognitive development with good results at school. Patients 2 and 3 had mild cognitive impairment. Patient 2 had poor school performance and Patient 3 had learning difficulties and delayed speech. The clinical presentation of each patient at the start of laronidase therapy is summarized in Table 1.

All patients had abnormalities on MRI, namely dilated ventricles, cystic areas of decreased signal on T1-W (predominantly in the periventricular white matter), which appeared hyperintense on T1-W and T2-W sequences. Patient 2 had mild abnormalities but normal white matter signal (Fig. 1A).

Patients 1 and 2 had previously received neurosurgical treatment at age 10 and 8, respectively. Patient 1 underwent C2–C5 laminectomy for cervical spine compression. Patient 2 had undergone insertion of a ventriculo-peritoneal shunt.

Treatment and assessments

Patients 1, 2 and 3 started weekly infusions of laronidase at the recommended dose (100 U/kg or 0.58 mg/kg) at ages 14, 11 and 3.5 years, respectively, and had been treated for 4.5, 4 and 3.5 years at study entry.

Cognitive function assessments were performed by the same experienced child psychologist (V. Barbier) at baseline and annually thereafter using the Wechsler Intelligence Scale for Children (WISC III) for Patients 1 and 2 and the Weschler Preschool and Primary Scale of Intelligence-III (WPPSI-III) for Patient 3.

Clinical assessments were as follows: general physical condition (Childhood Health Assessment Questionnaire, CHAQ), joint mobility, 6-min walking test, eye and retina examination, ear, nose and throat (ENT) examination, orthopedic evaluation, bone X-rays, ECG, cardiac ultrasound, pulmonary capacity, and liver and spleen volume (assessed clinically and by ultrasound). Urinary glycosaminoglycans (GAG) and antibodies against laronidase were also monitored.

MRI was performed with a 1.5 T (Signa General Electric) scanner using the following sequences: sagittal spin echo (SE) T1, axial fast SE (FSE) T2 and coronal fluid-attenuated inversion recovery (FLAIR) images. MRI was performed before the onset of ERT and annually thereafter.

Results

General outcome

Table 2 summarizes the clinical outcome for Patients 1, 2 and 3 at 4.5, 4 and 3.5 years after the start of ERT. All three patients showed improved joint mobility and displayed better exercise tolerance. Sleep apnea improved in Patient 3 and lung obstructive disease in Patient 2. Liver and spleen volume normalized in Patient 3. No marked changes in auditory or other sensory functions were observed except for a marked improvement in visual acuity in Patient 1. No adverse events were observed. Urinary GAG normalized within two months of starting ERT treatment. Anti-laronidase antibodies were positive in Patients 2 and 3 at moderate levels (1/100) compared to other treated MPS I patients, and remained negative in Patient 1.

Cognitive performance

Patient 1, who had an intelligence quotient (IQ) within the normal range at baseline, showed stable scores in IQ tests during ERT therapy. Patients 2 and 3 exhibited significant improvement in cognitive performance from the second year of ERT onwards, with increases of 13 and 29 IQ points, from baseline to 33 and 39 months post-ERT, respectively (Fig. 2). Patient 2 who had educational difficulties improved significantly her school performances. Patient 3 was under school age when he started treatment. He entered primary school 18 months after treatment onset, and had excellent results so far.

MRI changes

Patients 1 and 3 showed an improvement on MRI scans performed at 17 and 45 months after the onset of ERT, respectively, characterized by a reduction of white matter hyperintensity (Patients 1 and 3) and a reduction of cystic images of the periventricular white matter (Patient 1). Ventricular dilatation remained stable. In Patient 2, white matter signal appeared normal on all MRI scans performed up to 27 months after onset of ERT (Fig. 1A). The improvement in MRI pathological findings was similar to those observed in an MPS I-Hurler patient who underwent HSCT at age two (Fig. 1B).

Discussion

It has been proposed that patients with attenuated MPS I have only restricted or no neurological impairment because there is residual α-L-iduronidase activity in the brain [10]. However, most of these patients display abnormalities of the brain on MRI scans. The white matter signal changes observed primarily in patients with Hurler's syndrome can also be present in some individuals with the attenuated Scheie or Hurler–Scheie phenotypes, and may be the result of demyelination, gliosis, or accumulation of foamy cells [11,12]. MRI changes have been observed in MPS I patients, such as increased signal intensity in the periventricular white matter, cribriform changes (involving peri- and supra-ventricular, parietal and white matter, corpus callosum, and basal ganglia), ventricular enlargement and atrophy [13]. There is, however, no clear correlation between MRI abnormalities and the severity of neurological involvement in untreated MPS I patients [13]. It is interesting, though, that in Hurler patients successfully treated by HSCT favorable neurological outcomes are accompanied by MRI improvements, as illustrated in the patient included here for comparative purposes (Fig. 1B) and reported by other authors

Table 1
Key clinical characteristics at the start of enzyme replacement therapy (ERT).

Patient 1	Patient 2	Patient 3
Aged 14 years	Aged 11 years	Aged 3.5 years
Joint stiffness	Joint stiffness	Coarse features
Chronic fatigue	Exertion fatigue	Joint stiffness
Visual loss due to optic nerve compression	Headache	Dysostosis multiplex in X-rays
	Tinnitus	Hepatosplenomegaly
Headache	Carpal tunnel syndrome	Recurrent ENT infections
Tinnitus	Moderate mitral prolapsed	Carpal tunnel syndrome
Moderate mitral prolapse	Moderate obstructive lung	Moderate sleep apnea (no requirement for surgery or non-invasive ventilation)
Carpal tunnel syndrome	disease (a few cough and wheezing episodes in winter)	