

Long-term enzyme replacement therapy in a severe case of mucopolysaccharidosis type II (Hunter syndrome)

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Abstract. – Hunter syndrome or mucopolysaccharidosis II (MPS II) is a rare X-linked disease caused by a deficiency of the iduronate-2-sulphatase (I2S) lysosomal enzyme, resulting in a progressive accumulation of glycosaminoglycans (GAGs). Enzyme replacement therapy (ERT) with recombinant human I2S idursulfase has been used infrequently in children <5 years. We present the case of a 7 years and 10 months-old child, who was diagnosed with a severe form of MPS II at the age of 3 years, and who began a 36 months' treatment with idursulfase at 4 years 10 months. After 10 months, GAG urinary excretion was normal, but after just 4 months the liver and spleen had decreased in size, returning to normal limits by 36 months. Significant bone remodeling was noted after 16 months. Cardiac and neurological development, however, progressively deteriorated. The only adverse reactions were episodic inflammations of the upper and/or lower respiratory tract, but there was no otitis. Early use of ERT, presuming good treatment adherence, can significantly improve bone abnormalities.

Key Words:

Enzyme replacement therapy, Iduronate-2-sulphatase, Mucopolysaccharidosis type II, Idursulfase.

Introduction

Mucopolysaccharidosis type II (MPS II) is a deficiency of the lysosomal enzyme iduronate-2-sulphatase (I2S), which is required for the breakdown of glycosaminoglycans (GAGs) dermatan sulfate and heparan sulfate¹. Unlike other forms of MPS which are autosomal recessive, MPS II is X-linked. The estimated prevalence of MPS II is 1/170,000 live male births¹.

The accumulation of GAGs in nearly all tissue types and organs is progressive. The clinical phenotype is characterized by macrocephaly, coarse facies, stocky build, hepatosplenomegaly, retinal degeneration, hearing loss, cardiomyopathy, repeated upper respiratory tract infections associated with an elevated risk of airway obstruction, especially during sleep¹⁻³, and multiple skeletal dysostoses^{4,5} such as thoracolumbar hump, squared metacarpals, thickened and enlarged ribs and clavicles, valgus knee, and arthropathy of the hips^{6,7}. Severe forms are characterized by progressive neurological damage, and death usually occurs in the first or second decade of life, due often to respiratory or cardiac complications¹⁻³.

At present there is no standard treatment for the disease. Stem cell transplantation to provide enzyme activity sufficient to slow down or stop the progression of the disease was not as successful as expected⁸⁻¹¹. More encouraging results have been achieved with enzyme replacement therapy (ERT) with idursulfase (Elaprase, Shire HGT Pharmaceuticals, Cambridge, MA, USA), which is recombinant human I2S². There are limited data regarding the use of idursulfase therapy in children under 5 years of age^{12,13}. We report the case of a male child with severe MPS II aged 7 years and 10 months who received long-term treatment with ERT beginning before 5 years of age.

Case Report

History

He is an only child of non-blood related parents, born at the end of gestation by eutocic delivery weighing 3.250 kg ($\geq 25^{\text{th}}$ percentile) and 49cm in length ($\leq 25^{\text{th}}$ percentile). As related by

the parents, his growth and neuro-motor development appeared normal up to the age of 3 years, but he had late language development and motor instability. After an initial neurological examination for these symptoms, he was hospitalized for further investigation because of suspicion of a metabolic disease.

Examination

Clinical examination at the age of 3 years revealed difficulty in extending his knees beyond 170 degrees and the presence of a systolic murmur at the apex. An echocardiogram detected a mild thickening of the mitral and aortic flaps with mild mitral stenoin sufficiency and aortic stenosis, and mild inferior-posterior pericardial effusion. Radiography of the carpus and hands revealed “bullet” metacarpals, of the spine showed anterior “beaking” of the vertebral somas at L1, L2 and L3, and of the pelvis indicated dysmorphism (Figure 1a). Abdominal ultrasound indicated an enlarged but structurally unaltered liver and spleen, which on further examination via magnetic resonance imaging (MRI) had a volume of 710.9 cc (>2 standard deviations [SD]) and 172.1 cc (>5 SD), respectively. Brain MRI revealed a mild increase in the size of the cisterns of the base and the ventricular cavities, accompanied by an increase in the size of periencephalic subarachnoid spaces, particularly in the frontal-temporal area, consistent with cerebral atrophy and delayed myelination. There were minute hy-

perintense lesions in the bilateral posterior periventricular regions. His cognitive development was assessed using the Brunet-Lezine scale; at the age of 3 years and 3 months his mental age was 2 years and 1 month. He had no corneal opacities.

MPS II was confirmed by biochemical and genetic analysis at the age of 3 years and 4 months. The dimethylmethylene blue test showed elevated urinary GAG levels (400 mg GAG/g creatinine; normal range for age: 22-86 mg GAG/g creatinine). Enzymatic assay from cultured fibroblasts indicated low I2S activity (0.83 nmol/mg/4h; normal range 36±9 nmol/mg/4h). The activity of β-glucuronidase was normal (130.9 nmol/mg/h; normal range 97.3±29.9 nmol/mg/h), while the activity of α-iduronidase was elevated (241.3 nmol/mg/h; normal range < 148 nmol/mg/h). Genetic analysis of the I2S gene identified one splice site mutation (c. 418+1 G>C).

At the age of 4 years and 10 months he presented with pain in his left hip and limping. Pelvic radiography (Figure 1b) showed increased articular space because of effusion. The bone structure was altered due to the presence of radiotransparent areoles, corresponding to areas of re-absorption of bone tissue, alternated with dense areas attributable to filling of bone trabeculae. The patient’s scapulo-omeral and elbow articulation were also assessed, by comparing the passive range of motion (ROM) with those considered to be physiological¹⁴.

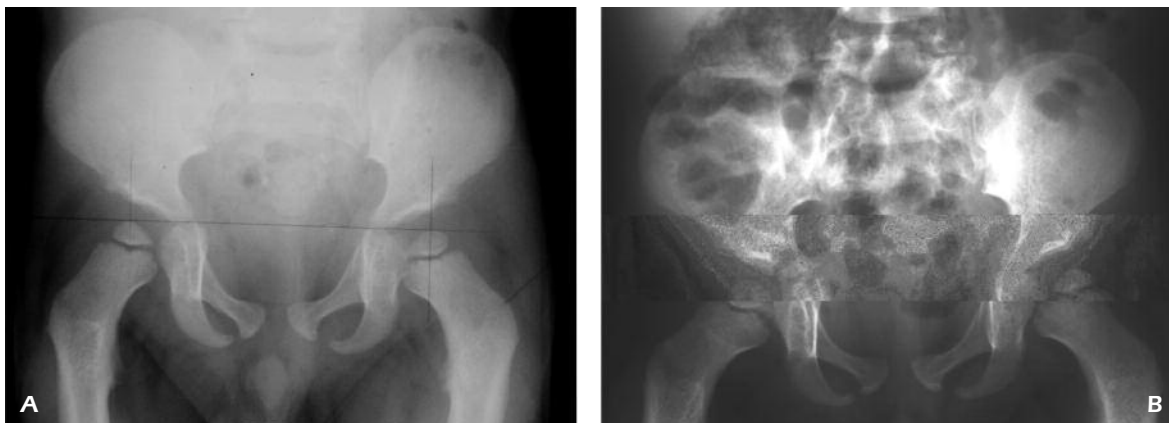


Figure 1. Pelvic radiography pre-treatment (**A**) at age 3 years and 5 months. Note the reduced dimensions, dysmorphic and lateralized femoral epiphyseal nuclei and the mild increase in the slope of the roofs; and (**B**) at age 4 years and 10 months. Note the reduction in dimension of the left femoral epiphyseal nucleus, which shows radio transparent areoles of bone reabsorption of its margins, present also in the subchondral area, adjacent to the cartilage of growth. There is articular effusion to the left and a tendency to extrusion of the cephalic nucleus, as well as a mild reduction in the slope of the right acetabular roof.

Treatment

After the initial echocardiogram, treatment with aspirin tablets was started at a dosage of 100 mg/day and continued for 2 months following regression of pericardial effusion. Treatment with intravenous idursulfase 0.5 mg/kg weekly began in August 2006 when the patient was aged 4 years 10 months. Orthopedic specialists advised against anti-inflammatory and orthopedic treatment.

Outcome

One month after treatment initiation, urinary GAG excretion was reduced to 152 mg GAG/g creatinine, and was within the normal range by 10 months (15.2 mg GAG/g creatinine; Figure 2).

Compared with their volume at diagnosis, the liver and spleen were noticeably smaller 4 months after treatment (assessed via ultrasound), and by the end of treatment (CT scan) had decreased in volume to within the range of healthy children.

Radiographic pelvic examination during 3 years of treatment revealed progressive changes as follows. At 4 months after treatment commenced, there was a reduction in left articular effusion, although the fragmented aspect of the proximal epiphyseal nucleus remained (Figure 3a). At 10 months after initiation of treatment, there was complete disappearance of the indirect signs of articular effusion and an increase in the radiographic density of the left epiphyseal nucleus (Figure 3b). Clinical examination at this time point revealed that the patient had joint stiffness, difficulty in walking, an evident limp,

and the right knee was mildly flexed. At 16 months (Figure 3c) there was re-calcification of the proximal femoral cephalic nucleus, and a bilateral modest reduction in the size of the cervical-diaphyseal angles, which was expected because of adaptation to a more erect posture. After 2 years there was a complete recalcification of the left femoral cephalic nucleus, although small internal areas of radio-transparency were present (Figure 3d). At the end of treatment (3 years' duration), pelvic radiography (Figure 3e) and a computed tomography (CT) scan (Figure 3f) suggested further re-calcification of the left femoral cephalic nucleus. The acetabular bone conformation was good at right, sufficient at left, and the CT scan did not show any significant bilateral articular effusion.

ROM assessment of scapulo-omeral, elbow and lower limb (hips, knees, ankles) articulation was conducted every 6 months during treatment. There was a rapid initial improvement in ROM of the hips and knees followed by stabilization. We noted a very mild improvement in flexion, extension and pronation of the elbow but supination of the elbow alternated between remission and aggravation. The change in scapulo-omeral articulation during 3 years of treatment followed a sinusoidal pattern, with a mild final improvement compared with baseline.

At treatment end, echocardiogram results were unchanged versus pre-treatment.

On the Vineland scale, his neurological developmental age was 1 year and 7 months when his chronological age was 7 years and 3 months.

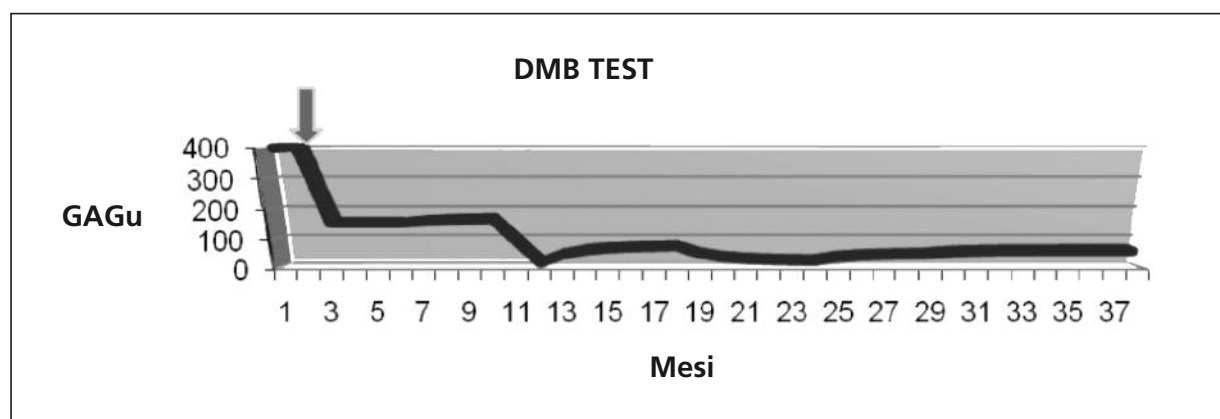


Figure 2. Urinary glycosaminoglycan (GAGu) levels pre-treatment and every month during treatment with enzyme replacement therapy (ERT). GAGu was assessed by dimethylmethylene blue tests and units are in mg GAG/g creatinine. The arrow shows the commencement of ERT.



Figure 3. Pelvic radiography showing changes during treatment with idursulfase. **(A)** At age 5 years 2 months (4 months' treatment). Note the centering of the right femoral head has improved further. The "fragmented" aspect of the left epiphyseal nucleus continues, with an increase in the slope of the acetabular roof. **(B)** At age 5 years 8 months (10 months' treatment). Note the increase in dimension and "radiographic density" of the left epiphyseal nucleus, and disappearance of indirect signs of left articular effusion with better conformation and slope of the acetabulum. **(C)** At age 6 years 2 months (16 months' treatment). Note the further mild increase of density of the left femoral epiphyseal nucleus and partial bilateral reduction off the femoral cervical-diaphyseal angle. **(D)** At age 6 years 10 months (24 months' treatment). Note the left femoral cephalic nucleus is almost completely re-calcified, with a quite regular femoral head profile. There is good acetabular bone conformation to the right and sufficient to the left, where a minimal lateralization of the cephalic nucleus has persisted. **(E)** At age 7 years 9 months (final examination after 36 months treatment). **(F)** Computed tomography scan at same time as radiograph shown in (e). Note the left femoral cephalic nucleus with re-calcification, mildly lateralization, moderately density and small internal geodesic cavities.

Final clinical examination showed that the patient was shorter than average, (<3rd percentile), had a normal body weight (>50th percentile), a large cranium (>97th percentile), coarse facial features with a large tongue, a barrel thorax, a protruding abdomen, slightly flexed knees and arthritic hands. His articular movements were reduced, with widespread rigidity, and he walked on the tips of his toes.

Long-term ERT was well tolerated, and no adverse reactions were identified except for occasional episodic inflammation of the upper and/or lower respiratory tract. This episodic inflammation occurred more frequently during winter months. The patient did not experience any episodes of ERT-related otitis, nausea, vomiting, abdominal pain or diarrhea.

Discussion

In the previous 2 years the therapeutic approach toward MPS II has changed. Hematopoietic stem cell transplantation (HSCT), used in subjects with varying disease severity, can modify the progression of visceral, skeletal and somatic abnormalities⁸⁻¹¹, but does not halt the progression of neurological damage in more severe cases^{8,15,16}, and is associated with a high risk of morbidity and mortality^{9,17}.

ERT is an important new option for the treatment of patients with MPS II². In a key phase II/III trial of ERT in patients with MPS II, there were substantial reductions in hepatosplenomegaly and urinary GAG excretion and significant improvements in 6 minute walking distance and respiratory function after 1 year of treatment¹⁸. In contrast to HSCT, adverse reactions associated with ERT were mostly of mild severity, the most frequently reported being fever, headache, pharyngitis, cough, infections of the upper respiratory tract, nasal congestion, nausea, vomiting, abdominal pain and diarrhea¹⁸. Most treatment-related adverse reactions were infusion reactions¹⁸.

In our patient, most improvements in the signs and symptoms of MPS II were consistent with those known to take place with ERT^{2,3}. There were somatic improvements, but little improvement of cardiac abnormalities, height, and enlargement of the head, and neurological deterioration was not halted^{2,3}. We also noticed a mild rehabilitation of articulation of the upper limbs, but this was temporary, probably because of poor treatment compliance.

Long-term treatment was well tolerated in our patient. We, therefore, consider that treatment commencement at this young age, at least in the case of our patient, did not represent an increased risk of adverse reactions. In fact, it has been recommended that where possible, treatment is started early in the course of the disease².

Improvements in bone abnormalities, particularly of the hip were of most interest in our case. Arthropathy of the hip in MPS II tends to take the form of a dysplasia with sub-dislocation of the femoral head and increase in the cervical-diaphyseal angle ("coxa valga") associated with defects in the calcification of the acetabulum and/or of the superior and lateral portion of the femoral head¹⁹.

Our patient had "Perthes-like" alterations, with bilateral and asymmetric involvement, as well as unusual involvement both of the acetabulum and the femoral heads. His hip arthropathy did not progress towards the typical radiological aspects of "coxa magna" or "coxa plana"⁵. Moreover, after an initial progressive reduction of the "density" of the bone segments early in ERT treatment, this trend was reversed, and at the end of treatment, an unexpected re-calcification and remodeling of the proximal femoral cephalic nucleus with centering of the femoral head was observed.

Conclusion

Early commencement of ERT in the case of a severe form of MPS II modified the natural evolution of the disease. The effects of re-calcification and bone tissue remodeling were also significant, with a restoration of mobility. On the contrary no effect was found relating to the cardiac and neurological development, as expected, and his height remained stunted. We believe, however, that ERT early in the disease can significantly improve bone abnormalities by taking advantage of the more rapid bone turnover which is typical of the first decade of life.

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