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Case Report

30 months follow-up of an early enzyme replacement therapy in a severe Morquio A patient: About one case

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ABSTRACT

Patients under 5 years were not evaluated in the phase-3 study for enzyme replacement therapy (ERT) in MPS IV A. Here we describe the evolution of a severe Morquio A pediatric patient who was diagnosed at 19 months old and treated by ERT at 21 months old for the next 30 months.

Applying the standard ERT protocol on this very young patient appeared to reduce his urinary excretion of glycosaminoglycans (GAGs); the improvements in both the 6 minute-walk test (6MWT) and the stair climb test, however, were no different than those reported in the nature history study. Additionally, this young patient experienced many ERT-associated side effects, and as a result a specific corticosteroid protocol (1 mg/kg of betamethasone the day before and 1 h before the ERT infusion) was given to avoid adverse events. Under these treatments, the height of this patient increased during the first year of the ERT although no more height gain was observed thereafter for 18 months. However, despite of ERT, his bone deformities (including severe pectus carinatum) actually worsened and his medullar cervical spine compression showed no improvement (thus needed decompression surgery).

Conclusion: early ERT treatment did not improve the bone outcome in this severe MPS IV A patient after the 30 months-long treatment. A longer term follow up is required to further assess the efficacy of ERT on both the motor and the respiratory function of the patient.

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1. Introduction

Morquio A syndrome (mucopolysaccharidosis IVA (MPS IVA); OMIM#253000) is a rare autosomal recessive lysosomal storage disorder caused by *N*-acetylglactosamine-6-sulfatase (GALNS) deficiency due to genetic mutations [1]. In severe cases, the patients can suffer from serious skeletal dysplasia characterized by vertebral platyspondyly, hip dysplasia and genu valgum. Until recently, apart from possible hematopoietic stem cells transplantation [2,3], the mainstay of the treatment remained symptomatic [4].

In 2014, the results of a phase-3 placebo-controlled trial indicated positive outcomes associated with using elosulfase alfa as an enzyme replacement therapy (ERT) for MPS IVA in both urinary excretion of glycosaminoglycans (GAGs) and 6 minute-walk test [5]. However, patients under 5 years old were not included in this study. Recently, to address younger patients' need, Jones et al. examined the effects of a 52 weeks-long ERT in 15 patients aged <5 years old; they found positive effects of ERT on patients' height compared to the natural history study (MorCAP) [6].

We report here the results of a 30 months-long ERT treatment in a severe case of Morquio A of 21 months old.

2. Clinical report

The patient is the second child of a consanguineous Moroccan family. The pregnancy and birth were uneventful (birth parameters: weight 3.2 kg; height 49 cm; head circumference 36 cm). He was seen at 19 months of age for thoraco-lumbar kyphosis and pectus carinatum. Initially, the child weighted 12.2 kg (75th percentile), heighted 81 cm (25th percentile) and had a head circumference at 53 cm (98th percentile).

The clinical examination showed typical bone deformities, no hepatosplenomegaly and neurological examination was normal. There

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was no corneal clouding on ophthalmologic examination. Initial X-rays showed costal widening, roster-shaped vertebra, widening and verticalization of the acetabulum, coxa valga and ovoid-shaped proximal femoral epiphysis. The patient was diagnosed with MPS IV A based on the results of (1) an increased urinary GAGs excretion (increased keratan sulfate), (2) a null GALNS activity in leucocytes, (3) the identification of homozygous c.871G>A mutation in GALNS gene — already described as responsible for a severe MPS IVA phenotype [7].

Elosulfase alfa treatment (2 mg/kg/week) was initiated for this patient at 21 months of life. During the 30 months-long ERT treatments, 3 administrations were missed due to fevers caused by the intercurrent diseases or surgery.

2.1. Biological efficacy

As we could not evaluate the blood levels of keratan sulfate (KS) and chondroitin-6-sulfate (C6S), and the urine level of C6S, we examined only the urinary keratan sulfate (uKS) during the course of the disease. Initially, uKS excretion was at 13 mg per mmol of creatinine (normal values: <4 mg/mmol creatinine). After 3 months of ERT, we observed a 72% decrease in uKS excretion; the level of uKs decrease reached 82% after 18 months and stabilized around 60% after 30 months of treatment (at 5 mg/mmol creatinine). We further noticed that the decreases in uKs were entirely dependent on the ERT since when the treatment was interrupted during one week for the vertebral surgery, uKS immediately increased; its level returned to pre-surgery values only after two weeks of ERT.

2.2. Clinical efficacy

2.2.1. Height (Fig. 1)

After 30 months of ERT, we observed an initial improvement of height (+10 cm in 12 months), but this evolution stopped and the height stabilized at 92 cm without any height gain in the last 12 months (Fig. 1).

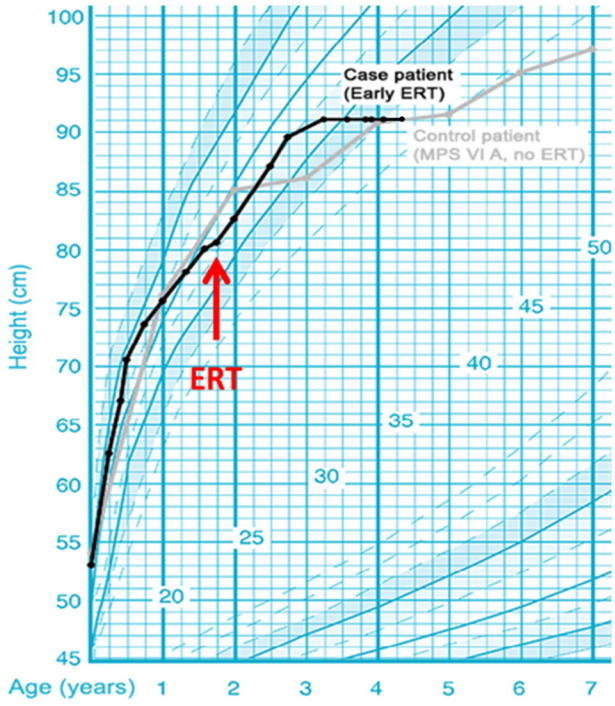

Fig. 1. Patient height (black line) compared to a MPS IV patient without ERT (gray line). Enzyme replacement therapy initiation (red arrow). French auxology reference curves [23]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.2.2. Bone and spine evolutions

The pectus carinatum and the kyphosis actually worsened during the 30 months of ERT although no limbs morphological change was detectable during the same period. Cervical cord compression (diagnosed on systematic medullar MRI) occurred despite of the treatment, and as a result, the child required surgical decompression after 13 months of ERT. The MRI control at 4 years old (after 27 months of ERT) showed continuation of slight medullary hypersignal, suggesting persistent medullar involvement due to the cervicothoracic junction kyphosis. The diameter of the cervical canal, however, remains stable.

2.2.3. Functional parameters (motor and respiratory functions)

We performed the 6 minute-walk and the stairs climbing tests every year once the child acquired the ability to walk. We observed improvements in walking distance and in stairs climbing of the patient every year (Table 1). Respiratory functions test were not done because of the young age of the child

2.2.4. Liver, spleen and cardiac follow-up

Abdominal and cardiac ultrasounds were normal at diagnosis and remained normal throughout the treatment period.

2.2.5. Neurocognitive development

Neuropsychological follow-up (WPPSI IV) showed normal cognitive development.

2.3. Safety

The ERT in this young patient induced frequent adverse events such as vomiting, chills, tremors and fever despite medications, including dexchlorpheniramine (anti-histamine), acetaminophen, and corticosteroids given 1 h prior to ERT infusion. However, the child presented a severe adverse events after 16 months of ERT (shock necessitating emergency management by fluid infusion and corticosteroid administration). We then modified the pre-treatment to betamethasone at 1 mg/kg po the day before and 1 mg/kg iv 1 h before ERT. Since this time, the patient never presented any further adverse events. The posology of betamethasone administered the day before was progressively decreased after 8 months without adverse events, and was stopped 16 months after the beginning of this protocol.

3. Discussion

The management of Morquio A syndrome has until recently been limited to supportive and symptom-based care [4]. Some experiences [2,3] in HSCT have been published without clear improvement in height outcome; for example, in the study of Yabe et al. [3], 4 cases of Morquio A patients had undergone HSCT, the youngest patient, who suffered a severe form of the disease and had the HSCT at 4 years old, showed no clear improvement on growth as his final height at 18 years old was only 112 cm [3]. At present, the first line treatment is the enzyme

Table 1
6 minute-walk test and stair climbing test at 6, 13 and 30 months of ERT.

	Nov 2013	July 2014	Feb 2015	July 2016
Age (months)	21	27	34	46
ERT (months)	0	6	13	30
6-Min walk test				
Distance (m)	*Walking not acquired*	209	217	*257*
Heart rate (/min)		172	165	135
Saturation (%)		98	96	97
Stairs climbing test				
Number of stairs (min)	*Walking not acquired*	10 (1′22)	22 (2′)	*44 (2′23)*
Heart rate (/min)		168	157	130
Saturation (%)		100	96	100

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