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Clinical report

Clinical response to long term enzyme replacement treatment in children, adolescent and adult patients with Hunter syndrome

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ABSTRACT

Background and objective: Since enzyme replacement treatment (ERT) with idursulfase is available for Hunter syndrome (HS; mucopolysaccharidosis type II), for the first time, disease progression can be limited and organ damage reduced or prevented.
Patients and methods: We described retrospectively the clinical evolution of eight HS males, treated with ERT and followed in routine clinical practice in Hospital Infantil La Fe (Valencia, Spain).
Results: We studied three children, three adolescents and two adults. Time from diagnosis to ERT ranged from 13.7 to 0.2 years, and duration of ERT ranged from 24 to 77.1 months. From the start of ERT, weight and height increased in children and adolescents and remained stable in adults. Glycosaminoglycans (GAG) decreased in all patients; in patient 5 (aged 23 years), we observed the highest reduction (86%) with recovery of carpal tunnel syndrome, splenomegaly and a decrease in nocturnal oxygen dependence.
Conclusion: Our results show that ERT improve respiratory impairment and organomegalies and decrease GAGs levels in all patients including children, adolescent and adults. While cardiac manifestations and facial features stabilized, responses in other parameters were heterogeneous.

Respuesta clinica al tratamiento prolongado con terapia de reemplazo enzimático en niños, adolescentes y adultos con Síndrome de Hunter

Palabras clave:
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Idursulfasa
Esplenomegalia
Sindrome del tunel carpiano
Obstruccion de vias aereas

RESUMEN

Introducción y objetivo: Desde que la Terapia de reemplazo enzimático (TRE) con Idursulfasa está disponible para el Síndrome de Hunter (SH; mucopolisacaridosis tipo II) la progresión de la enfermedad puede limitarse y posiblemente reducir y prevenir el daño orgánico.
Pacientes y métodos: Describimos retrospectivamente la evolución de 8 pacientes con SH, tratados con TRE y revisados según práctica clínica habitual en el Hospital Infantil La Fe (Valencia, España).
Resultados: Estudiamos 3 niños, 3 adolescentes y 2 adultos El tiempo desde el diagnóstico hasta inicio de TRE fue de 0,2 a 13,7 añosy la duración de la TRE de 24 a 77,1 meses. Tras iniciar la TRE, el peso y la talla de los niños y adolescentes se incrementaron permaneciendo estable en los adultos. Los glucosaminoglicanos (GAG) disminuyeron en todos los pacientes; la mayor reducción (86%) se observó en un adulto que mejoró el túnel carpiano, disminuyó la esplenomegalia y la dependencia nocturna de oxígeno.
Conclusión: Nuestros resultados muestran que la TRE mejora la función respiratoria, las organomegalias y reducen los niveles e GAGs urinarios en todos los pacientes incluyendo niños, adolescentes y adultos. Las manifestaciones cardiacas y facials permanecieron estables. Los resultados en otros parámetros fueron heterogeneos.

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Introduction

Mucopolysaccharidoses (MPS) are lysosomal storage disorders (LSD), caused by deficiency in enzymes involved in degrading glycosaminoglycans (GAG).[1,2]

MPS type II, or Hunter syndrome (HS) is a rare X-linked LSD characterized by deficiency in the activity of the lysosomal enzyme iduronate-2-sulfatase (I2S), owing to a mutation in the I2S gene (IDS) which results in the lysosomal accumulation of glycosaminoglycans (GAGs) leading to cell, tissue, and organ dysfunction.[3–5]

HS incidence is between 0.69 and 1.19 per 100,000 live births,[3,6–8] has a variable onset age and progression rate,[8] including a wide spectrum of phenotypes, with variable clinical severity.[1,5] Life expectancy depends on disease severity; patients with severe phenotypes die before their 20s, whereas individuals with attenuated forms may survive into their 50s or 60s.[8,9]

Central nervous system (CNS) involvement is associated with progressive neurological deterioration, and worse overall health.[3] Based on neurological manifestations, patients are classified in three groups: (1) without CNS involvement; (2) with mild or moderate CNS involvement and (3) with severe CNS impairment.[4]

The first effective ERT for HS[10] is idursulfase (Elaprase®, Shire Pharmaceuticals), available in Spain since 2007.[3] Idursulfase has shown to be safe and effective in improving respiratory function, joint mobility, and walking ability.[2,3,11–15] To date, the ERT effects on cardiac abnormalities are unclear.[2,16,17]

The relationship between progressive GAG storage and clinical manifestations provides a strong argument for the initiation of ERT as early as possible following diagnosis.[18]

International registries such as Hunter Outcome Survey (HOS) collect information of patients from several countries.[3,8,19,20] Thus, based on parameters with the best quantitative response to ERT, Clinical Guidelines have been published.

However, recommendations are not available in some hospitals.[21]

Therefore, we performed the present study collecting qualitative information, with long term follow-up, based on routine clinical practice to describe the results in Hunter patients management of a pediatric referral hospital, from the beginning of ERT availability.

Methods

Retrospective study of HS patients treated with ERT (idursulfase) from 2007 in Hospital Infantil Universitario La Fe (Valencia, Spain).

ERT was administered according to Summary of Product Characteristics (0.5 mg/kg/week).

All patients were diagnosed by residual enzyme activity and pathogenic mutation description.

Clinical evaluations were conducted following routine protocols according to normal standards of care of HS in the center. Collected information included: family history, weight and height, blood pressure and heart rate, spleen and liver sizes (cm), previous surgeries (adenoidectomy, hernia repair, ear tubes, tonsillectomy), signs and symptoms, urinary GAGs, concomitant medications, spirometry (FVC: forced expiratory vital capacity; FEV1: forced expiratory volume), electrocardiogram, echocardiography, brain imaging (by magnetic resonance imaging, MRI), audiometry, joint mobility, 6-min walk (6 MW), and overnight sleep study (polysomnography).

Quality of life was measured using the Hunter Syndrome-Functional Outcomes for Clinical Understanding Scale (HS-FOCUS) questionnaire, that contains six functional status domains: Walking/Standing, Reach/Grip, Sleeping, Schooling/Work, Activities and Breathing. Higher scores correspond to a higher degree of incapacity.[22]

Results

Eight male patients with an established diagnosis of HS were included. Four of them were relatives: two brothers aged 18 and 16 year-old (patients 1 and 2), and their cousins, two brothers of 23 and 16 year-old (patients 3 and 4). Summary of baseline characteristics including mutation analysis is shown in Table 1 Average age for starting ERT ranged between 2.3 and 20.2, and duration of ERT ranged from 24 to 77.1 months (Table 1).

Patient's growth

From the start of ERT, adolescents increased their weight and height, and the most notable increase was observed in patient 2 (from 37.0 to 47.4 kg after 17 months of treatment), Patients 1, 2 and 4 had an increase of 5.5–6.5 cm in height, while younger patients (6, 7 and 8) increased their height by 4.5–5 cm/year. Weight and height remained stable in adult patients (Figs. 1 and 2).

Cardiovascular signs and symptoms

No homogeneous trends were observed in patients during ERT. Valvular involvement was present in most patients (Table 2). Patient 5 showed an increase in the PR and QRS intervals during ERT (PR interval: from 161 to 192 ms. QRS interval from 65 to 110 ms) and a decrease in LVM (left ventricular mass) index (from 200.1 to 107.6 g/m$^{2.7}$).

Facial features and ear, nose and throat (ENT) symptoms

Typical coarse facial features of HS were observed in all patients, and these remained stable during ERT (Table 2).

Ear symptoms were present in all patients including hearing loss, ventilation tubes and chronic and acute otitis media. Improvement of hearing problems (auditory evoked potentials in patient 5) was reported in most patients after ERT, avoiding the presence of ventilation tubes (which were necessary in patients 6 and 7) (Table 2).

Skeletal and neurological signs

Skeletal signs (stiffness of joints, kyphosis, claw hands and pain) persisted during ERT, while mild improvement was observed in patient 8 (Table 2).

Carpal tunnel syndrome was present in all patients (except patient 8), while it was mild in patients 6 and 7 and severe in patient 5 (improved after 12 months of ERT).

No differences were observed in 6 MW. Adolescent patients presented a normal motility before treatment, without significant differences during the follow up. Notably, patient 5, who had the greatest symptom impairment, was able to walk approximately 200 m, and doubled the distance after 2 years of treatment.

Respiratory improvements

Pulmonary function could not be assessed in younger patients.

Spirometry testing showed a restrictive ventilatory pattern at baseline in patients 1 (FEV1/FVC = 87.0) and 3 (FEV1/FVC = 84.6) (Table 3).

Increases in FEV1 (%) and FVC were reported in all patients and two of them (patients 2 and 4) achieved a normal FEV1 range (80–120%).