

## **Mutation c.1190-1delG/N in intron 8 and c.1708G>C/N in exon 12 not reported in the *IDUA* gene developed a clinical phenotype of Scheie syndrome.**

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**Keywords:** Scheie syndrome, *IDUA*, c.1190-1delG/N, c.1708G>C/N.

**Abstract.** Mucopolysaccharidoses are a group of lysosomal storage disorders caused by deficiency of enzymes catalyzing the degradation of glycosaminoglycans. Mucopoly-saccharidosis I can present a wide range of phenotypic characteristics with three major recognized clinical entities: Hurler and Scheie syndromes represent phenotypes at the severe and mild ends of the clinical spectrum, respectively, and the Hurler-Scheie syndrome is intermediate in phenotypic expression. These are caused by the deficiency or absence of  $\alpha$ -L-iduronidase, essential to the metabolism of both dermatan and heparan sulfate, and it is encoded by the *IDUA* gene. We report the case of a 34-year-old male patient with enzymatic deficiency of  $\alpha$ -L-iduronidase, accumulation of its substrate and a previously unreported mutation in the *IDUA* gene that developed a phenotype of Scheie syndrome.

**Mutación c.1190-1delG/N en el intrón 8 y c.1708G>C/N en el exón 12 no reportada en el gen de *IDUA* desarrolló un fenotipo clínico de síndrome de Scheie.**

*Invest Clin* 2014; 55(4): 365 - 370

**Palabras clave:** síndrome de Scheie, *IDUA*, c.1190-1delG/N, c.1708G>C/N.

**Resumen.** Las mucopolisacaridosis son un grupo de trastornos de almacenamiento lisosomal causada por la deficiencia de enzimas que catalizan la degradación de glicosaminoglicanos. La mucopolisacaridosis tipo I puede presentar un amplio rango de características fenotípicas englobadas en tres entidades clínicas reconocidas: los síndromes de Hurler y Scheie representan los fenotipos graves y leves del espectro clínico, respectivamente y el síndrome de Hurler-Scheie intermedio en la expresión fenotípica. Estos son causados por la deficiencia o ausencia de la  $\alpha$ -L-iduronidasa esencial para el metabolismo del dermatán y el heparán sulfato y es codificada por el gen *IDUA*. Se presenta el caso de paciente masculino de 34 años de edad con deficiencia enzimática de  $\alpha$ -L-iduronidasa, acumulación de su sustrato y una mutación en el gen *IDUA*, no reportada previamente, que desarrolló un fenotipo del síndrome de Scheie.

*Recibido: 25-11-2013 Aceptado: 5-6-2014*

## INTRODUCTION

The first description of patients recognized as mucopolysaccharidosis (MPS) cases was made by Charles Hunter in 1917. He described two Canadian sibs, both boys, affected by a similar disease, characterized by coarse facies, large abdomen, bone dysplasia and other signs and symptoms. Two years later, Gertrud Hurler, a German pediatrician, reported two unrelated boys with similar clinical findings. She described the visceromegaly and bone abnormalities present in the patients. Many similar cases were described subsequently and the term "gargoylism" was used for some time, due to its resemblance to the images of medieval cathedrals gargoyles. In 1962, an American ophthalmologist described an attenuated form of this syndrome, based on the corneal opacity observed in an adult patient. This condition was first referred to as Scheie syndrome, but later was incorpo-

rated within the MPS I spectrum. After the diseases were fully identified in terms of their biochemical and molecular bases, it became clear that a large clinical variability is present within each MPS type, with severe and attenuated forms (1).

The MPS are a group of lysosomal storage disorders caused by deficiency of enzymes catalyzing the degradation of glycosaminoglycans and characterized by intralysosomal accumulation and increased excretion in urine of partially degraded glycosaminoglycans, which ultimately results in cell, tissue and organ dysfunction (2). Hurler syndrome (OMIM 607014) is the most common and severe form of MPS. Its incidence has been reported to be 1:100.000 in live births and no predilection for sex and ethnicity has been found. Presents an autosomal recessive trait, due to deficiency or absence of lysosomal hydrolase-iduronidase enzyme activity encoded in the *IDUA* gene, which has been

mapped in 4p16.3. Deficiency of this enzyme results into a wide range of phenotypes including Hurler syndrome, Hurler-Scheie syndrome (OMIM 607015) and Scheie syndrome (OMIM 607016), severe, intermediate and mild forms, respectively (3). We report a male patient with clinical diagnosis of Scheie syndrome, enzymatic deficiency of  $\alpha$ -L-iduronidase, accumulation of its substrate and a mutation not previously reported.

### CLINICAL REPORT

A 34-year-old Venezuelan male is the first son of healthy non consanguineous parents with unremarkable family history. At 7 years of age, began a history of progressive stiffness in the upper and lower limbs and claw-hand deformity. At 26, presented muscle weakness, frequent falls, myalgia and generalized arthralgia. Diagnostic of blurred vision and corneal opacity in ophthalmologic evaluation was realized. He underwent surgical repair for umbilical hernia.

At clinical examination, weight was 51.5 kg (3th centile), height 159 cm (<3th centile and SDS-2,6), head circumference 57 cm (50th-75th centile). Coarse facies, prominent forehead, synophrys, downslating palpebral fissures, anteverted nose, bulbous nasal tip, short columella, thick lips, short neck, chest symmetric and abdomen without organomegaly. There was evidence of limited joint movements of the upper limbs, claw-hand (Fig. 1); and thick skin. The mental development was normal.

Magnetic resonance imaging examinations of the spine showed compression of the cervical cord secondary to glycosaminoglycans accumulation in the dura (Fig. 2) and degeneration, with prominent fibrous rings L4-L5 and L5-S1 with spinal stenosis and conditioned segmental hypertrophy of facet joints. Echocardiography ex-



Fig. 1. Claw-hand deformity.



Fig. 2. Magnetic resonance imaging of the spine shows compression of the cervical cord secondary to GAG accumulation in the dura (pachymeningitis cervicalis).

hibited trivial mitral fibrosclerosis and mitral insufficiency. Renal ultrasound showed bilateral micro nephrolithiasis

Electrophoretic urinary glycosaminoglycans showed one band corresponding to the migration of dermatan sulfate. Decreased activity of the enzyme  $\alpha$ -L-iduronidase in leukocytes was determined through a fluorometric method: 0.01 nmol/min/mg (reference value 0.31 to 0.71 nmol/min/mg) and dried blood spot on filter paper: 0.8  $\mu$ mol/l/h (reference value > 2.5  $\mu$ mol/l/h). Molecular analysis of the *IDUA* gene detected a mutation deletion type of guanine at the splicing site c.1190-1delG/N heterozygous in intron 8 and a second mutation wrong direction c.1708G> C/N, p. D570H/N heterozygous in exon 12, resulting in a change from histidine to aspartic acid at position 570 of the enzyme.

## DISCUSSION

MPS are a group of genetic disorders due to deficiency of lysosomal enzymes resulting in impaired glycosaminoglycans metabolism. The disorders have heterogeneous clinical phenotypes including natural history and symptoms among patients with the same type of MPS (4). Hurler syndrome patients have marked cognitive delay, coarse facial features, corneal clouding, hearing impairment, ear-nose-throat infections (5), cardiac disease and respiratory complications are common, hepatosplenomegaly, umbilical and inguinal hernias, restricted joint mobility and orthopedic defects. Without appropriate treatment, their life expectancy is severely limited (4).

Hurler/Scheie syndrome is characterized by progressive somatic involvement with dysostosis multiplex, corneal clouding, joint stiffness, deafness and valvular heart disease; but little or no mental retardation. Nevertheless, the onset of these symptoms occurs much later than on the Hurler syn-

drome and lead to significant impairment and loss of function (2). Cardiac and respiratory complications may limit life expectancy (2, 5).

Scheie syndrome presents with symptoms much later and slower disease progression (6). Patients have normal intelligence and near-normal life expectancy but experience significant morbidity as a consequence of restricted joint mobility, carpal tunnel syndrome and skeletal dysplasia (5). Also have pachymeningitis cervicalis (compression of the cervical cord secondary to glycosaminoglycans accumulation in the dura), claw-hand deformity, genu valgum, painful feet and *pes cavus*. Cardiac and respiratory complications are much milder than in the Hurler syndrome, with aortic and mitral valvular disease being a common feature (2). However, this traditional subtype classification is not based on precisely defined criteria and is not interpreted in a consistent fashion by all practitioners (6). Early diagnosis is due to the different treatment options available (7), among these, the hematopoietic stem cell transplantation and enzyme replacement therapy (8). This latter treatment is currently being received by the patient for more than two years, showing improvement.

Functionally,  $\alpha$ -L-iduronidase is essential to the correct metabolism of both dermatan sulfate and of heparan sulfate (2, 9), hydrolyzing the terminal  $\alpha$ -L-iduronic acid residues. The *IDUA* gene spans approximately 19kb and contains 14 exons mapped to 4p16.3 (2). Although some genotype-phenotype correlations have been established, most known disease-causing mutations -over 100 to date- (Human Gene Mutation Database; <http://www.hgmd.org>), are individually unique and uncharacterized (9, 10).

Biochemical studies on the patient indicated the accumulation of dermatan sulfate in urine and also the decrease in activity of the enzyme  $\alpha$ -L-iduronidase in leuko-

cytes and peripheral blood dry drop. Two mutations in the *IDUA* gene were found, one in intron 8, splice site c.1190-1delG/N, p.Q70X, which has a high prevalence in the severe clinical forms (9, 11). The second mutation was introduced into the exon 12, c.1708G>C/N, p.D570H/N, in heterozygous form, which has not been reported previously in the literature. According to the bioinformatics program SIFT the impact of this alteration in the structure and function of the protein predicted deleterious alteration with score 0.01 and according to the PolyPhen to predict structural and functional damage in proteins by mutations change sense, predicts probable damage with score 0.995.

The phenotype of MPS I have a continuous spectrum ranging from severe, moderate to mild findings. The patient studied in this report, presented clinical involvement since the first decade of life with slowly progressive joint disease and without abnormalities in cognition. The deficiency of the enzyme  $\alpha$ -L-iduronidase and the accumulation of its substrate were demonstrated. Furthermore, molecular analysis of the *IDUA* gene showed a mutation known in severe phenotypes and other mutation not reported previously in a patient with Scheie syndrome.

#### ACKNOWLEDGMENTS

We thank the Dr. Marina Szlagoof the Neurometabolism Consultory in Buenos Aires, Argentina for the determination of activity of the enzyme  $\alpha$ -L-iduronidase in leukocytes and peripheral blood dry drop and Dr. Graciela Serebrinsky of the Laboratory of Biology of Molecular Pathology in Buenos Aires, Argentina for molecular analysis.

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