

Case Report

## Hurler-Scheie syndrome with subclinical hypothyroidism: A case report

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### Abstract

Hurler-Scheie syndrome is an intermediate form of mucopolysaccharidosis (I H/S) and an autosomal recessive disorder caused by the deficiency of the enzyme L-iduronidase. We present the case report of a 7-year-old girl referred to us for evaluation of developmental delay with difficulty in walking, first detected at an age of 5 years. She was born to consanguineous parents with no family history of mucopolysaccharidoses. She had coarse facial features, short stature, hepatomegaly and her X-ray findings were consistent with mild form of dysostosis multiplex. Enzyme assay revealed deficient alpha-L-iduronidase activity in leukocytes. In addition to Hurler-Scheie syndrome, thyroid function tests indicated subclinical hypothyroidism with normal titers of thyroid microsomal and thyroglobulin antibodies. Hurler-Scheie syndrome with subclinical hypothyroidism is uncommon and has not been reported as yet.

**Keywords:** Hurler-Scheie, mucopolysaccharidoses, L-iduronidase

### 1. Introduction

Mucopolysaccharidoses Type 1 (MPS 1) (Hurler, Online Mendelian Inheritance in Man (OMIM) 607014; Hurler Scheie, OMIM 607015; Scheie, OMIM 607016) is a lysosomal storage disorder caused by deficiency of the enzyme L-iduronidase (alpha-L-iduronidase; E.C # 3.2.1.76). It is inherited as an autosomal recessive disorder and has an estimated incidence of 1 case per 100 000 live births.<sup>1,2</sup> The clinical features and course of MPS I are highly variable and consists of progressive multisystem involvement affecting respiratory, cardiac, skeletal, ophthalmologic, and in some cases central nervous system function.<sup>3</sup> Historically, patients have been categorized into 3 phenotypes with no objective means of delineation: Hurler (early onset, rapidly progressive, neurodegenerative), Scheie (later onset, less rapid progression, no neurodegeneration), and Hurler-Scheie (onset and progression between Hurler and Scheie extremes, with mild or absent central nervous system involvement).<sup>4</sup>

We present a case of Hurler-Scheie with subclinical hypothyroidism, diagnosed on the basis of the clinical features and confirmed by enzymatic assays.

### 2. Case Report

A 7-year-old girl presented with a history of growth retardation associated with difficulty in walking and with a limitation of extension of the elbows of 2 years duration. She was the third child of her consanguineous parents (first-degree cousins) with no family history of MPS 1. Her past medical, drug and social histories were unremarkable.

At the time of our initial evaluation, her weight was 13 kg and height 99 cm, both below the 3rd centile. She had a short neck and coarse facial features with hypertelorism. Her Intelligence quotient (IQ) was assessed using Binet Kamat test and found to be 74.72, indicating borderline IQ. Orthopedically there was mild flexion contracture in both elbows with functional range of movements, mild abdominal distension. Ultrasonography showed hepatomegaly and echocardiography (ECG) revealed tricuspid aortic valve leaflets, mild aortic regurgitation and left ventricular hypertrophy.

Skeletal examination revealed thickened calvarium in the posterior apex, macrocephaly, J shaped sella and beaked upper lumbar vertebrae. Enzyme assay for  $\alpha$ -L-iduronidase in leukocytes confirmed the absence of the enzyme (Normal value = 15-81 nmol/hr/mg). Thyroid function tests showed hypothyroidism with elevated thyroid stimulating hormone, normal free triiodothyronine and normal free thyroxine, associated with normal titres of thyroid microsomal and thyroglobulin antibodies while other biochemical test results of blood were unremarkable.

### 3. Discussion

The clinical presentation of our patient clearly correlated with type 1 MPS. Cases of attenuated MPS I vary widely with respect to age of presentation, symptoms, co-morbidities, and disease course. Many patients with attenuated MPS I survive into adulthood, with significant morbidity.<sup>1&2</sup>

Our patient was born of a consanguineous marriage and without a family history of similar disease in the past two generations. She had progressive somatic involvement including dysostosis multiplex, with little intellectual dysfunction. She had most of the features suggestive of Hurler Scheie syndrome which includes age of onset, short stature, corneal clouding, coarse facial features, hepatosplenomegaly, enlarged tongue, and valvular heart disease except, mental retardation, micrognathia, carpal tunnel syndrome and upper air way obstruction. Radiological changes seen in this child typify the constellation of skeletal abnormalities in Type 1 mucopolysaccharidoses known as dysostosis

multiplex.<sup>1</sup> The main radiographic features of dysostosis multiplex are shown in [Figure – 1 & 2]. Thyroid function tests showed elevated thyroid stimulating hormone, normal free triiodothyronine and normal free thyroxine associated with normal titers of thyroid microsomal and thyroglobulin antibodies indicating subclinical hypothyroidism. The clinical feature to support hypothyroidism is coarse skin, short stature and mark hirsutism was present all over the body.

**Figure 1 Hand-wrist skiagram. Arrows show bullet-shaped phalanges with proximal pointing of the second to fifth metacarpals.**



**Figure 2. Skull skiagram with arrow showing J-shaped sella.**



The diagnosis was confirmed by a analysis of urinary GAG with cetyltrimethylammonium (CTMA) bromide tests and by measurement of  $\alpha$ -L-iduronidase enzyme activity in serum.

Measurement of urinary glycosaminoglycan levels is a sensitive but nonspecific screening test for MPS I. False-negative results may occur, especially if the urine is too dilute (specific gravity of 1.015 g/mL).<sup>6,7,8</sup> Testing of enzyme activity in dried blood spots on filter paper has the added advantage of being easier to transport and handle. Enzymatic activity <10% of average reference values is compatible with MPS I diagnosis, and each laboratory must determine its own reference values. Measuring the activity of another lysosomal enzyme in the same sample is recommended for control of preservation of the material. Measurement of  $\alpha$ -L-iduronidase activity in cultivated chorionic villus or amniocytes is routinely used in pre-natal MPS I diagnosis.<sup>9</sup>

A definitive diagnosis of MPS I is based on deficient  $\alpha$ -L-iduronidase activity in fibroblasts, leukocytes, serum, or blood spots.<sup>1</sup> Pseudodeficiency of  $\alpha$ -L-iduronidase has been described but is rare and is not associated with increased urinary glycosaminoglycan levels.<sup>10</sup> The gene encoding  $\alpha$ -L-iduronidase has been mapped to the 4p16 site on chromosome 74(10) and has 14 exons of 19 kb and a large intron of 13 kb separating the second from the third exon.<sup>11,12</sup>

The frequency of MPS I alleles varies among ethnic populations. Among Caucasian patients, the W402X and Q70X alleles are found in 50% of patients with MPS I; these alleles are rare among Japanese, Korean, or Moroccan patients.<sup>13</sup> Patients who are homozygous for a nonsense allele or have 2 different nonsense alleles have the severe form of MPS I. Most patients with attenuated disease have missense mutation. Patients who have a p.R89Q or c.678-7g3a (IVS 57g3a) allele in association with a null mutation typically have an attenuated phenotype. More than 30 polymorphisms or nonpathogenic sequence variants in the iduronidase gene have been detected. These sequence variants may modify the severity of the clinical disease if they are present with a pathogenic MPS I allele.<sup>14,15</sup>

One of the mutations described in the  $\alpha$ -L-iduronidase gene, A300 T, causes pseudo-enzymatic deficiency, a situation in which there is an apparent enzyme deficiency *in vitro* yet not *in vivo*, which may lead the physician to making a false diagnosis. When it is based solely on enzyme levels.<sup>10</sup>

Treatment for MPS I was palliative and symptom-based. The hematopoietic stem cell transplantation (HSCT) and, enzyme replacement therapy (ERT) has heightened the need for better disease recognition, early diagnosis, and up-to-date comprehensive guidelines for disease management and treatment. Laronidase (Aldurazyme) is an enzyme produced by recombinant DNA technology is used solely and exclusively for treating patients with a confirmed diagnosis of MPS1.<sup>16</sup> Long-term ERT with laronidase restores sufficient enzyme activity to hydrolyze the accumulated substrate and prevent its subsequent accumulation.<sup>17,18</sup>

#### 4. Conclusion

The diagnosis of MPS I is possible with molecular methods in approximately half of the patients. In the remaining patients, gene sequencing must follow biochemical diagnosis to identify the mutation present. Detection of the mutation allows pre- and post-natal molecular diagnosis, and detecting heterozygotes allows for facilitating individual and family genetic counseling. As enzyme replacement therapy is not possible in our setup, we advised regular follow-up and symptomatic treatment.

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