

# MUCOPOLYSACCHARRIDOSIS TYPE 1 AND THE CHALLENGES IN MANAGING THIS RARE GENETIC DISORDER IN THE RESOURCE POOR SETTING

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## ABSTRACT

This case report is about a six-year-old Nigerian boy with a rare genetic disorder of attenuated mucopolysaccharidosis type 1 and the challenges that the clinicians face in managing these patients in resource poor settings. This patient presented with short stature with skeletal deformities, poor speech and intellectual impairment. He also had features such as coarse facial features with macroglossia, lichenified, dry thick skin and hepatosplenomegaly. Delay in the diagnosis is a common problem with this rare genetic disorder. Confirmation of the diagnosis and providing the recommended disease-specific therapeutic options such as of enzyme replacement therapy and haematopoietic stem cell transplantation are the challenges that we face in managing these patients in the resource poor settings.

**Key words:** Hurler-Scheie syndrome, attenuated mucopolysaccharidosis type 1

## INTRODUCTION

Mucopolysaccharidosis type 1 (MPS 1) is a rare inherited lysosomal storage disorder caused by deficiency of the enzyme  $\alpha$ -L-iduronidase. It is an autosomal recessive disorder. The symptoms and signs of the disease entity are related to the pathological changes that occur with the accumulation of heparan sulfate and dermatan sulfate in various tissues of the body (1, 2). It is a progressive multisystem disorder with life-threatening complications. Based on the age of onset, the rapidity of progression and the presumed degree of cognitive involvement, MPS1 is clinically classified into three phenotypes; Hurler, Hurler-Scheie and Scheie syndromes, in descending order of severity (1, 2).

There is a great deal of overlap between each of these three syndromes and there is no strict clinical, biochemical or molecular diagnostic criteria in place to differentiate them (3). As a result, MPS 1 is currently divided into two major types based on clinical severity; the severe and the attenuated types (4). Homozygous nonsense mutation of the IUA gene results in severe MPS 1 (Hurler syndrome) whereas missense mutation on the same gene results in attenuated MPS 1 (Hurler-Scheie and Scheie syndromes) (5). The clinical manifestations include facial dysmorphism, hepatosplenomegaly, upper airway obstruction, skeletal deformities and cardiomyopathy. Common cutaneous findings are the lichenified, dry, thick skin with diminished elasticity, increased pigmentation on the dorsum of the hands, scleroderma-like changes,

hypertrichosis of the extremities, pale-coloured hair and alopecia areata (1). It has been observed that there are significant variations in clinical manifestations among individual patients and patients in different parts of the world (6, 7). The mostly involved organs are the bone, the viscera, the connective tissue and the brain (1). Although the disease is potentially fatal, it is treatable (7). The diagnosis is primarily based on the physician's recognition of signs and symptoms (3).

The diagnosis of MPS is suggested by certain clinical and radiological findings (dysostosis multiplex). Dysostosis multiplex manifests as changes in the skull, thorax, pelvis, hands and spine (2). Mucopolysaccharides are present in urine and can be detected by urine analysis. Confirmation of the diagnosis is by the assessment of enzyme activity in leucocytes or cultured skin fibroblasts.

This is a rare genetic disorder with an estimated global prevalence rates of 1:100,000, 1:300,000, 1:1 000,000 newborns for Hurler, Hurler-Scheie and Scheie syndromes respectively (8). In the US, severe MPS 1 occurs in 1 in 100,000 newborns and attenuated MPS 1 occurs in 1 in 500,000 newborns (4). An epidemiological study done by Beck et al involving 987 patients from four regions of the world (Asia Pacific, Europe, Latin America and North America) to find out the distribution of MPS 1 phenotypes has demonstrated that the 60.9% of the patients were Hurler, 23% of the patients were Hurler-Scheie, 12.9% of the patients were Scheie and 3.2% were undetermined (7). However, there is limited epidemiological data available from African region.

A report from Murphy et al has shown that from a series of 31 patients (14 females and 17 males), 26 had Hurler syndrome, 4 had Hurler-Scheie syndrome and one had Scheie syndrome (1). In another retrospective epidemiological study conducted in Estonia over a period of 22 years, did not find any case of MPS 1 (9).

The purpose of this report is to describe a rare case of attenuated type MPS 1 (Hurler-Scheie syndrome) affecting a six-year-old Nigerian boy and to discuss the challenges of management in a resource-limited setting.

## CASE REPORT

This is a six-year-old Nigerian boy who presented with deformity of the spine and limbs for 3 years, poor speech for 2 years and a progressive decline in reading ability for one year. His developmental milestones have been within normal limits before the onset of symptoms. Family history was non-contributory. There was no history of prolonged neonatal jaundice or delayed passage of meconium. The patient has been seen on various occasions by different physicians, at least five times in the past one year for recurrent respiratory infections. Except for some learning disabilities, his mental status assessment did not suggest any intellectual impairment

His height was 91.5cm (<3rd percentile) with an arm span of 104cm. The upper segment of the body was 47.5cm with an upper segment-lower segment ratio of 1.1:1. He also had skeletal deformities such as kyphosis (gibbus), pigeon chest deformity, limited extension of the knee and elbow joints (Figures 1). There was a limitation of abduction of the shoulder joint and short stubby digits with limited extension. He had a large dolichocephalic head with frontal bossing with flat nasal bridge. He also had soft tissue changes such as macroglossia and thick lips. His skin was lichenified, dry, and thick with diminished elasticity. He had an umbilical hernia and hepatosplenomegaly. The stretched penile length was 6cm and the testicular volume was 2ml. He had a deep hoarse voice. There was no cardiac murmur on auscultation.

Based on clinical features, a clinical diagnosis of attenuated mucopolysaccharidosis type 1 (Probable Hurler-Scheie syndrome) was made. Cretinism (congenital hypothyroidism), the main differential diagnosis was excluded by the normal thyroid function tests. Urine screening test for acid mucopolysaccharides (dermatan and heparan sulfates) and confirmatory enzyme activity assay for  $\alpha$ -L-iduronidase were not performed because of the unavailability of these laboratory facilities in our centre.

## DISCUSSION

The diagnosis of attenuated MPS 1 is based on the age

of onset, relatively slow progression, presence of corneal clouding, hepatosplenomegaly, stiff joints, clinical evidence dysostosis multiplex, coarse facial features, hernia and normal thyroid function test results. Although we could not perform radiological studies in our patient, the presence of changes in the skull, thorax, hands and spine were suggestive dysostosis multiplex in our patient (2). The above clinical features are present in more than 90% of the patients with attenuated MPS 1 (6).

Hurler-Scheie syndrome is the commonest MPS 1 found in Brazil and Chile but not in the other Latin American countries (6). However, no data is available from Africa for comparison. The age of onset for MPS 1 varies from 1 to 8 years and according to the world figures, the mean age of onset of symptoms is about 2.2 years (5, 6). However, the age of onset of this disease is very much lower (about 1 year) in Latin American countries (5), reflecting a significant difference in clinical manifestations between regions. The age of onset of the symptoms in our patient is about 3 years, which is in keeping with the world figure.

Hurler-Scheie syndrome is characterized by mild or no cognitive impairment and relatively severe somatic symptoms. If untreated, the life expectancy is limited to the second or third decade (10). According to the reports from India, the short stature is also a common problem in these patients (11, 12). However, in patients where the age of onset of symptoms is after 5 years, short stature is not prominent and the intelligence level is usually normal (5). In contrast, the onset of symptoms is during infancy and the short stature and cognitive impairment is a rule rather than an exception in Hurler syndrome.

The delay in diagnosis of this rare genetic disorder is very common. There was a significant delay in the diagnosis of the index patient despite consulting a physician on several occasions with recurrent respiratory tract infections. This is not surprising for a rare disease with this nature of phenotypic heterogeneity (3) and this is mainly attributed to the lack of awareness among physicians regarding this rare genetic disorder (10, 13).

Managing the patients with MPS 1 is a challenge. Unavailability of diagnostic facilities and the recommended disease specific treatment options such as enzyme replacement therapy and hematopoietic stem cell transplantation are the main challenges (14). Early diagnosis and determination of phenotype are important to determine the best treatment option for each MPS 1 patient (6). Currently, two non-mutually exclusive disease-specific therapeutic options are available for MPS 1 haematopoietic stem cell transplantation and enzyme replacement therapy (4, 10) and neither of these two therapeutic options are available in the resource poor settings like ours.

In conclusion, MPS 1 is a rare autosomal recessive genetic disorder that could leads to fatal complications.

Early diagnosis and appropriate treatment can improve the lives of these patients. However, early diagnosis of this condition and implementation of appropriate treatment has been a challenge in a resource poor setting.



**Figure 1: Shows some of the clinical findings such as thick lips, umbilical hernia, and bony deformities such as chest deformity, large dolicocephalic head with frontal bossing. Elbow, wrist and knee joints are held in flexion due to contracture.**

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