Abstract

Hurler syndrome is one of the rare genetic disorders involving disturbances in mucopolysaccharide metabolism resulting in their increased accumulation in the lysosomes. This leads to a progressive disorder involving multiple lysosomes that often results in death by second decade of life. This disease, which has several oral and dental manifestations, is first diagnosed on the basis of clinical findings and then confirmed on the basis of enzyme assay. The purpose of present article is to emphasize the early diagnosis of MPS I, so as to enable the patients to utilize the available treatment modalities to reduce morbidity.

Keywords:
Hurler syndrome, mucopolysaccharides, alpha-L iduronidase, autosomal recessive.
Introduction

The mucopolysaccharidoses (MPS) is a rare group of genetic disorders involving disturbances in mucopolysaccharide metabolism. The incidence is 1:1, 00,000 births. Mucopolysaccharides (formerly called) or glycosaminoglycans (GAGs) are normal component of cornea, cartilage, bone, connective tissue and reticuloendothelial system and are therefore the target organs for deposition leading to multi-organ dysfunction and damage. Disturbances in ten known enzymes give rise to seven distinct types of MPS. MPS follow an autosomal recessive mode of inheritance, with the exception of MPS II which is inherited as an X-linked recessive trait. MPS I has further three subtypes. Hurler’s syndrome (MPS I-H) is the prototype of MPS. Other two subtypes are MPS I H-S (Hurler-Scheie syndrome) and MPS I S (Scheie syndrome) listed from most to least severe form. It is a lysosomal storage disorder caused by deficiency of alpha-L-iduronidase enzyme, resulting in interference with cellular function because of excess accumulation of partially degraded GAGs like chondroitin sulfate and heparan sulfate within the cells.

Case Report

A previously diagnosed case of MPS I in a 3 year old boy with coarse facial features was referred to our department by a pediatrician with a complaint of gingival enlargement for the last 3 months. Patient achieved normal milestones till the age of one year, but later on a progressive deterioration was noticed by the pediatrician. History of recurrent respiratory tract infections was reported, but the family history was non contributory. Child had stunted growth, lumbar gibbus, enlarged head, prominent forehead, saddle nose and hypertelorism with puffy eyelids (Figure 1). Hands were claw like with clubbing (Figure 2). Patient had protruded belly, everted umbilicus, hepatosplenomegaly and umbilical hernia. On intra oral examination open bite, generalized gingival enlargement with minimal clinically visible crown, high arched palate and macroglossia was observed (Figure 3). Delayed eruption of teeth was also noted. A panoramic radiograph could not be done as the child was not able to stabilize his head.

Chest radiographs showed kyphosis with oval vertebral bodies, having posterior scalloping and dorso-lumbar gibbus. Antero-posterior view revealed scoliosis, cardiomegaly, hepatomegaly and boat shaped ribs (Figure 4). Hand wrist radiograph revealed thickened diaphyses of radius and ulna with proximal tapering of metacarpels (bullet shaped) alongwith a coarse trabecular pattern (Figure 5).
Routine hematological examination revealed Hb % (12.5%) and ESR (6mm after 1 hour) within the normal limits, but an elevated TLC (24,700/ Cu mm) and altered DLC (Neutrophil =16 % and lymphocytes = 80 %) indicating towards chronic infection. Alpha L iduronidase enzyme assay revealed the absence of the enzyme from peripheral leukocytes. An echocardiogram done 6 months back revealed mild mitral regurgitation. Urine analysis revealed increased traces of iduronate sulfate and dermatan sulfate 6 months back. Oral home care advice was given and patient was referred back to the pediatrician for consideration of enzyme replacement therapy and bone marrow transplant.

**Discussion**

MPS I was previously divided into three separate syndromes, but as there is no clear cut distinction between them it is currently divided into severe (H) and attenuated (H/S & S) types only. Mutations in the *IDUA* gene, (chromosomal location 4p16.3) have been found to be associated with MPS I. The *IDUA* gene product IDUA enzyme is involved in the breakdown of large sugar molecules called GAGs. The lack of IDUA enzyme activity leads to accumulation of GAGs within cells, specifically in the lysosomes. The accumulation of GAGs increases in various organs leading to progressive enlargement and damage of those organs resulting in a constellation of symptoms.

Children often appear normal at birth as in the present case, although some may have umbilical or inguinal hernia. Severe MPS I cases generally begin to show other signs and symptoms of the disorder within the first year of life, while those with attenuated form have milder features that develop later in childhood. Other features include macrocephaly, hydrocephaly, heart valve abnormalities, coarse facial features, hepatosplenomegaly, and macroglossia. Vocal cords enlargement results in deep and hoarse voice. Airway obstruction in certain cases causes frequent upper respiratory tract infections, sleep apnea and difficulty in anesthesia. It is often associated with corneal clouding (vision loss), hearing loss and recurrent ear infections. Short stature and joint deformities are commonly associated. Dysostosis multiplex, (multiple skeletal abnormalities on radiographs) is associated with severe form of the disease. Cervical spinal stenosis can compress the spinal cord.
Figure 1: Extra-oral view with open bite, depressed nasal bridge, and gingival enlargement.

Figure 2: Enlarged belly with everted umbilicus.

Figure 3: Intra-oral view showing gingival enlargement, papillated tongue and crowns of deciduous maxillary canine.

Figure 4: Antero-posterior and lateral spine view radiograph.

Figure 5: Hand wrist radiograph.
MPS disorder is suspected based on clinical features, radiographic results or urinary screening tests, but definitive diagnosis are established by enzyme assay\(^2\).

Severe MPS I cases show a decline in intellectual function and a more rapid progression. Developmental delay usually presents by the age of 1 year, leading to loss of basic functional skills and eventually death by the age of 10 years\(^3, 4\). While attenuated MPS I survive till adulthood with/without learning disabilities. Heart diseases and airway obstruction are the major causes of death in MPS I \(^1, 3, 4\). In the current case, Dysostosis multiplex, recurrent respiratory tract infections and other features were observed, but corneal clouding was absent. Current management modalities include symptomatic relief, hematopoietic stem cell transplant and enzyme replacement therapy\(^4, 5\). To conclude, early diagnosis and multidisciplinary management of MPS can improve the quality of life of these patients.

References