Clinical Presentation and Diagnosis of Mucopolysaccharidosis Type 2 (Hunter Syndrome)

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Abstract

Introduction: We present a very rare case of mucopolysaccharidosis type II (Hunter syndrome), which presented as short stature, coarse facies, mild mental retardation with no corneal clouding and repeated upper respiratory tract infections. The purpose of presenting this case is to highlight the clinical manifestations specific to mucopolysaccharidosis type II (Hunter syndrome).

Case Presentation: A 20-years-old Indian male presented with short stature, coarse facial features, protruded abdomen with umbilical hernia with history of bilateral ear discharge. There was mild mental retardation and body joints were in flexed posture. Based on clinical presentation possibility of mucopolysaccharidosis is kept and based on 24 hr total urinary excretion of glycosaminoglycans (21.9 mg/mmolcreat; normal<8 mg/mmolcreat.), genotype analysis (revealing mutation p.Asp198Ala in exon 5 of Iduronidase 2 sulfatase gene), we diagnosed type 2 mucopolysaccharidosis (Hunter syndrome). We referred him to higher centre for enzyme replacement therapy.

Conclusion: Based on clinical findings and radiological features it is possible to diagnose a case of mucopolysaccharidosis. We treated him for his ear infection and offered him hearing aids thereafter we referred him to higher center for enzyme replacement therapy.

Introduction

Mucopolysaccharidosis (MPS) is a group of lysosomal storage disorders caused by the deficiency of the lysosomal enzymes needed to degrade glycosaminoglycans (GAGs). GAGs are oligosaccharide components of proteoglycans which provide structural integrity to connective tissues. Accumulation of partially degraded GAGs causes thickening of tissue and compromise of cell and organ function. This results in permanent, progressive cellular damage which affects the appearance, physical abilities, organ and system functioning and, in most cases, mental development. Common clinical presentation includes facial dysmorphism, hepatosplenomegaly, joint stiffness and contractures, pulmonary dysfunction, myocardial enlargement and valvular dysfunction and neurological involvement. We report this case of MPS type II because of its rarity and the clinical features of mild mental retardation, short stature, coarse facies, no corneal clouding and all other features suggestive of MPS type II. The purpose of presenting this case is to highlight the distinctive manifestation of Hunter syndrome.

Case Presentation

20 yrs old male, born of non consanguineous marriage admitted to our hospital with complaints of short stature and coarse facial features, thickening of palms and soles with protrusion of abdomen with umbilical hernia.

On history he has delayed mental, physical milestones without any significant birth history. He had poor scholastic performance. He had history of repeated episodes of bilateral ear discharge since childhood.

On detailed examination his head was dolichocephalic with depressed nasal bridge, hypertrichosis, thick large lips, macroglossia, increased gap in teeth, short neck, thick palms and soles, hallux valgus. Both upper and lower extremities stiff and in flexion. Abdomen protuberant and umbilical hernia present (Figure 1). Genital organs developed appropriate to age. He had mild hepatosplenomegaly with grade 2/6 non-radiating systolic murmur in the mitral area. Suspecting Mucopolysaccharidosis, we performed a skeletal survey. Anteroposterior and lateral X-rays of the skull showed an enlarged and J-shaped sella turcica (Figure 2). The bones of the skull and sutures appeared normal for his age. Anteroposterior and lateral X-rays of the dorsolumbar spine showed anterior beaking. X-rays of both hands showed his phalanges and metacarpals to be widened with proximal tapering of the metacarpals. An anteroposterior X-ray showed his ribs as wide with tapered posterior ends (a paddle and/or spatulated appearance) (Figure 3). Audiometry revealed bilateral conductive deafness and 2 D echo shows mild mitral regurgitation.

On the basis of 24 hrs total urinary excretion of glycosaminoglycans (21.9mg/mmolcreat; normal<8 mg/mmolcreat.), genotype analysis (revealing mutation p.Asp198Ala in exon 5 of Iduronidase 2 sulfatase gene), we diagnosed type 2 mucopolysaccharidosis (Hunter syndrome) with novel mutation.

Discussion

Mucopolysaccharidosis was first described by Charles Hunter, a Canadian physician, who in 1917 described a rare disease found in two brothers.1,3 Mucopolysaccharidoses are a group of inherited diseases characterized by defective lysosomal enzymes responsible for the degradation of mucopolysaccharides, which are major components of intercellular connective tissue. Hunter syndrome caused by deficiency of enzyme, iduronate-2-sulphatase.2 This leads to an accumulation of incompletely degraded mucopolysaccharidies in the lysosomes which affect various body systems through enzymatic activity.4 All MPS
are autosomal recessive, except Hunter syndrome which is X-linked recessive. In affected individuals, undegraded or partially degraded GAG accumulates within the lysosomes and is excreted in excess in the urine. The accumulation of GAG within the lysosomes is responsible for the clinical manifestation of this disorder.5

Mucopolysaccharidosis type II or Hunter syndrome is rare and is caused by a deficiency of iduronate-2-sulfatase. Hunter syndrome is one of the most common MPS with a prevalence of one in 170,000 male live births. MPS type II is classified into mild (type II, HB) and severe (type II, A) and this classification is based on the length of survival and the presence or absence of central nervous system (CNS) disease. Patients typically appear normal at birth in both types. In the severe form the clinical features appear between two and four years of age while in the mild form the clinical features appear in the second decade of life. In the severe form there is severe mental retardation and loss of skills. Death usually occurs in the first or second decade of life and the main cause of death is obstructive airway disease or cardiac failure. In the milder form there is mild mental retardation but intelligence is normal, stature is near normal, and clinical features are less obvious and progress very slowly. Diagnosis is usually made in the second decade of life. Death usually occurs in the fourth decade and the main cause of death is cardiac failure.

Diagnosis of the disease is usually made by clinical presentation and skeletal survey. The common clinical presentations are a large head (dolichocephalic), short stature, mental retardation, coarse facial features, a protuberant abdomen, a broad nose with flared nostrils, large jaws, hypotonia and a large tongue which becomes apparent between two and four years of age, and these clinical features were present in our case. Other clinical features include upper respiratory tract infection, valvular heart disease leading to right and left ventricular hypertrophy and heart failure, chronic diarrhea, enlarged liver and spleen, umbilical as well as inguinal hernia, corneal clouding with poor vision and hearing loss caused by both connective and sensorineural deficits. A communicating hydrocephalus is a common finding and can lead to severe manifestation of neurological signs which were not present in our case.

Analysis of GAGs (heparan and dermatan sulphates) is a screening test for MPS type II. The presence of excess heparan and dermatan sulphates in the urine is evidence of MPS type I, MPS type II or MPS type VII. Confirmatory diagnosis is by enzyme assay in leukocytes, fibroblasts or dried blood spots and plasma sample, using substrates specific for 12S. Absent or low 12S activity in males is diagnostic of Hunter syndrome, provided other sulfatase deficiency has been ruled out.

Enzyme replacement therapy using idursulfase (Elaprase), a recombinant human 12S produced in the human cell line, has been recently approved in the United States and the European Union for the management of MPS type II. Weekly intravenous infusion is given over three hours at a dose of 0.5 mg/kg diluted in saline. Bone marrow transplantation (BMT) and umbilical cord blood transplantation (UCBT) are definitive treatments for MPS. Apart from these, supportive management is very important. Physical therapy and daily exercise may improve mobility of joints. Blood transfusion, infection and nutritional management are also important in the management of MPS type II.

**Conclusion**

Based on clinical findings and radiological features it is possible to diagnose a case of mucopolysaccharidosis. 24 hrs urinary glycosaminoglycans estimation and genetic studies confirms the diagnosis and its type, which will help in offering enzyme replacement therapy to the given individual.
References


