

A Rare Case of Mucopolysaccharidosis: Hunter Syndrome

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ABSTRACT

Hunter syndrome, or mucopolysaccharidosis type II (MPS II), is a member of a group of inherited metabolic disorders together termed mucopolysaccharidosis (MPSs). It is a rare, X-linked disorder caused by a deficiency of the lysosomal enzyme iduronate-2-sulfatase. The prevalence of this syndrome is 1:100,000 births. Insufficient enzyme activity results in accumulation of glycosaminoglycans (GAGs) in the lysosomes of various tissues and organs and leading to progressive multisystem pathologies. Here, we report a case of 13-year-old boy who presented with typical facial, skeletal and dental features without corneal clouding. It is possible that thorough and systematic clinical and radiological examination alone can help in diagnosis of this complex disorder.

Keywords: Coarse facial features, Delayed eruption, Macroglossia

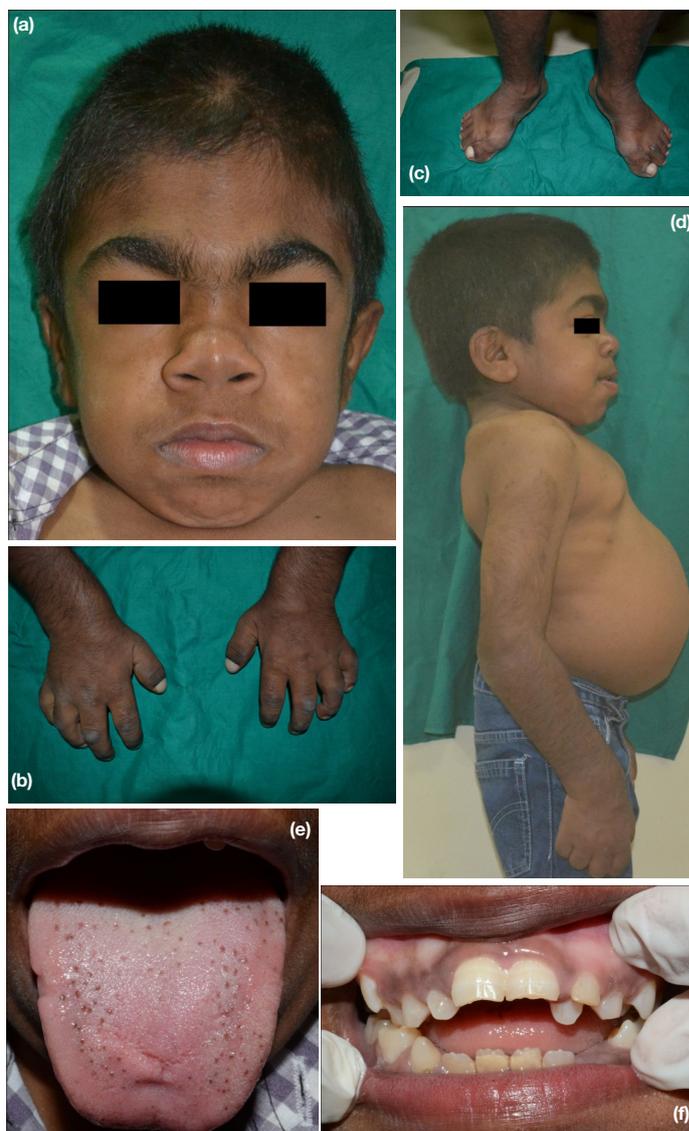
CASE REPORT

A 13-year-old boy reported to the out-patient Department of Oral Medicine and Radiology, K.V.G. Dental College and Hospital with a chief complaint of irregularly placed front teeth. Dental history did not reveal delay or early eruption of milk teeth. Patient's parents gave history of frequent episodes of seizures from the age of 8 year and also growth retardation from the age of 10 year. Medical history revealed surgery for inguinal hernia on right side at 9 year and left side at 12 year of age. The boy is the second of three children, eldest one being girl. His brother had similar complaint of inguinal hernia. Family history revealed early death of his mother's 2 siblings at the age of 13 year.

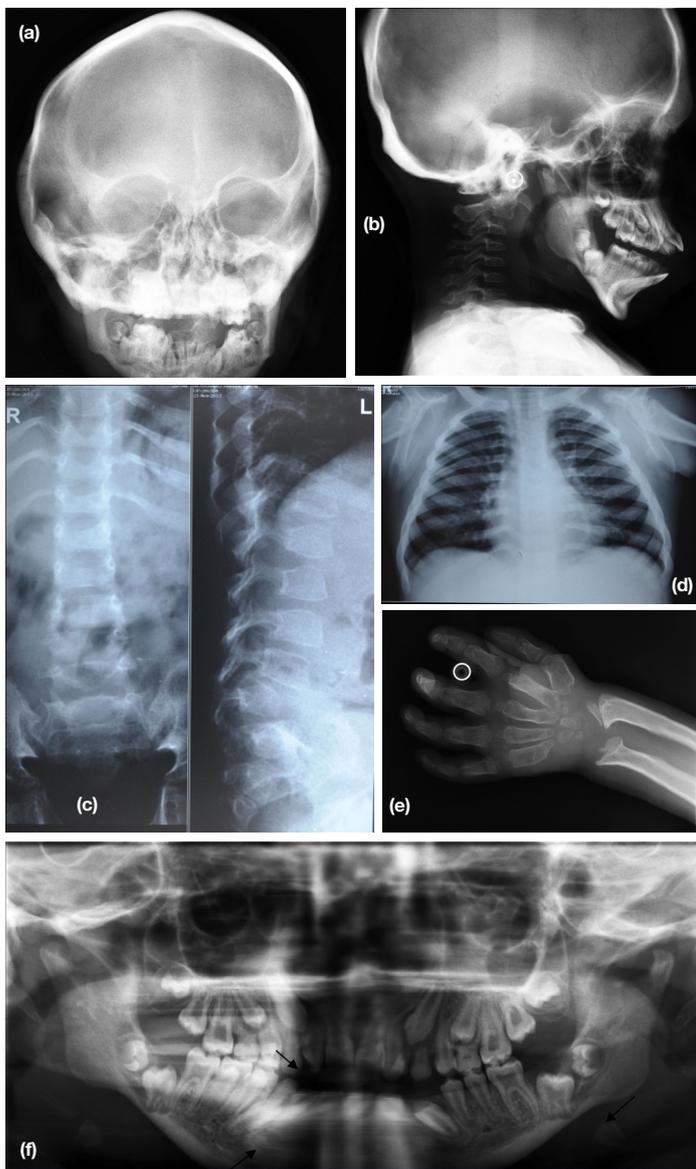
On general physical examination, patient was of short stature of height 116cm, arm span of 109cm and weight 25.2 kg. He had macrocephaly with bilateral temporal and frontal bossing, coarse facial feature, depressed nasal bridge with wide nostrils, bilateral periorbital oedema, bushy eyebrows, hypertelorism and puffy eyelids [Table/Fig-1a]. He was intellectually normal.

Examination of extremities and joints showed claw like hands and stiff joints. Skin of extremities was thickened and inelastic [Table/Fig-1b&c]. Physical examination also revealed protruded abdomen and hepatosplenomegaly [Table/Fig-1d]. Cardiovascular examination revealed systolic murmur in mitral area, best heard in grade 2 mitral area radiating to left auscultatory variable split to second heart sound. Ophthalmic examination revealed clear corneas without any corneal clouding. Intraoral examination showed incompetent lips, macroglossia, and anterior open bite [Table/Fig-1e&f]. Periodontal status and oral hygiene were good.

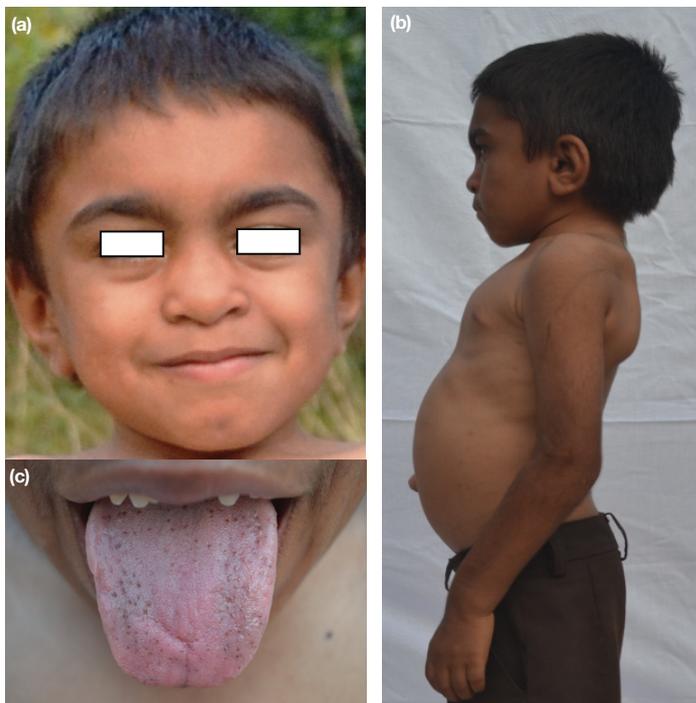
PA skull radiograph showed thickened skull vault with parietal protuberance bilaterally with a dolicocephalic shape [Table/Fig-2a]. Lateral skull revealed J-shaped sella turcica with thickened skull [Table/Fig-2b]. Ribs had oar-shaped configuration and thickened clavicles on the chest radiograph [Table/Fig-2c]. AP lumbosacral view revealed anterior beaking of lumbar vertebral bodies giving a gibbus deformity or focal kyphosis [Table/Fig-2d]. Hand wrist radiograph showed proximal pointing of metacarpals [Table/Fig-2e]. Panoramic radiograph showed multiple retained and impacted teeth, enlarged pulp chamber [Table/Fig-2f]. Urine analysis showed the presence of GAGs. Serum alkaline phosphatase level was increased to 539 IU/L and other hematological findings and renal function test were within normal limits.



[Table/Fig-1a-f]: (a) Shows typical coarse facial features, depressed nasal bridge with wide nostrils, bilateral periorbital oedema, bushy eyebrows and puffy eyelids. (b) Shows patient's claw like hand (c) Shows abnormal lower extremity of the patient (d) Shows protruded abdomen and chest (e) Intraoral photograph showing macroglossia (f) Intra oral photograph showing anterior open bite



[Table/Fig-2a-f]: (a) PA skull view showing thickened skull vault with parietal protuberance bilaterally with a dolichocephalic shape (b) Lateral cephalogram showing thickened skull vault and J shaped deepened sella turcica (c) Chest radiograph showing thickened clavicle with oar shaped ribs (d) AP spine view showing anterior beaking of lumbar vertebrae (e) Hand wrist radiograph showing proximal pointing of metacarpals (f) Panoramic view showing multiple retained and impacted teeth and enlarged pulp chamber



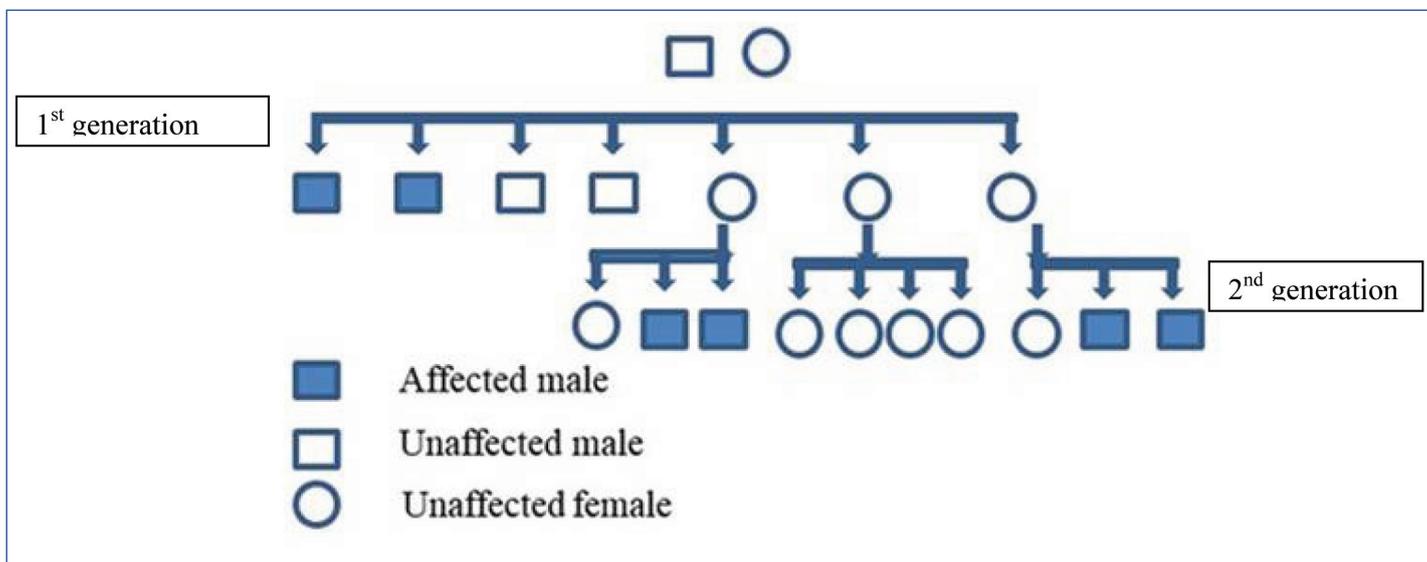
[Table/Fig-4a-c]: (a) Patient's sibling showing coarse facial features, depressed nasal bridge with wide nostrils, bushy eyebrows and puffy eyelids (b) Shows abnormal chest and abdomen (c) Shows macroglossia

Pedigree analysis chart of the patient's family is shown in [Table/Fig-3]. As mentioned in the chart, patient's grandparents were normal. Out of 4 boys and 3 girls of the family, 2 boys and all girls were unaffected. The 2 boys affected died at the age of 13 year. Out of the 3 females, two of them have girl children who are unaffected. Elder female who is the mother of our patient has 2 boys and a girl where 2 boys are affected while the girl was unaffected. Patient's sibling was showing certain milder facial features of the syndrome [Table/Fig-4a-c].

Patient was referred to physician for the evaluation of his general condition. Oral prophylaxis was done and patient was advised for a regular follow up.

DISCUSSION

First described by Major Charles Hunter in 1917, mucopolysaccharidosis type II (MPS II or Hunter syndrome; OMIM +309900) is an X-linked recessive disease [1].



[Table/Fig-3]: Pedigree chart of the patient showing x linked inheritance in the family

Hunter syndrome is a MPS with multiorgan and multisystem involvement that has an inconstant age of onset and a variable rate of evolution [1]. Seven phenotypes of MPS are caused by eleven separate single lysosomal deficiencies. Except for Hunters syndrome all of the MPS are inherited in autosomal recessive manner. Being X linked inheritance, Hunter syndrome affects males exclusively. A small number of female occurrence is also been well documented [2].

In Hunters syndrome, there is deficiency in the activity of lysosomal enzyme, iduronate-2- sulfatase (I2S). I2S is the enzyme which catalyzes the removal of the sulfate group at the 2 position of L-iduronic acid in heparan sulfate and dermatan sulfate. I2S is located at Xq28, and over 150 mutations have been found out [1].

New studies from Germany and the Netherlands report an incidence of 1 case in 140,000-330,000 live births, and 1.3 cases per 100,000 male births [2]. It can occur in any ethnic group; a slightly higher occurrence has been reported in the Jewish population living in Israel [3].

In Hunters syndrome, GAG is partially or even undegraded and get accumulated within the lysosomes and excrete in urine [3]. The accumulation of GAG in various organs gives a characteristic appearance to the affected individual and is called as gargoyles [4].

Based on the length of survival of the affected individual and the presence or absence of central nervous system abnormality two phenotypes exists: type A is the severe classic form and type B is the milder form. In type A, clinical features are apparent in the first year of life. Somatic and neurologic development will be slow with severe mental retardation. In this severe form, death occurs by adolescence due to cardio respiratory failure secondary to upper airway obstruction and cardiovascular involvement [1]. The milder form is characterised by manifestation of clinical features in the second decade of life. Patients present with mild mental retardation but intelligence is usually normal and other clinical features are less prominent and progression of the disease is very slow [5]. In patients with neurologic association, intelligence is reduced, and death usually occurs in the second decade of life, whereas those patients with minimal or no neurologic involvement may live into adulthood with normal intellectual development [6]. In our case, patient does not have mental retardation and is healthy till the age of 13 year which is in contrast to his affected family members who passed away at the age of 13. Hence, here we may assume that the patient belongs to a milder form and is under observation.

Hunter syndrome is most commonly presented with coarsening of facial features, which becomes apparent between 2 and 4 years of age. Macrocephaly, broad noses with flared nostrils, prominent supraorbital ridges, large jowls, thick lips and large tongue are the other common features. Due to the joint stiffness and contractures, mobility of joint is restricted [7]. Retinopathy, optic nerve atrophy and hypertelorism are the manifestations of ocular involvement. All these features are seen in our case which started at the age of 10 except retinopathy and optic nerve atrophy. The hearing loss is caused by both conductive and sensorineural deficits [8] which was absent in the present case.

Upper airway obstruction is the major contributing factor in mortality of the disease. This is mainly caused by weakening of the trachea or bronchial walls [9]. Restricted movements of the temporomandibular joints, stiffness of the chest wall, and abdominal distention also inhibit normal breathing. Short stature is thought to be due to a failure of endochondral ossification in growth plates secondary to GAG deposition. Severe restriction of motion can occur due to arthropathy affecting all joints. More vulnerable joints are hip joints and severe erosive hip dysplasia can be present [1].

GAG storage also characteristically leads to hepatomegaly and splenomegaly. Umbilical hernia is commonly observed, and inguinal

hernias are reported in 60% of male patients [9]. In our case both the patient and his younger brother was treated for inguinal hernia. Bladder obstruction and neurogenic urinary retention have been stated [10]. Severe behavioral disorders, such as over activity, obstinacy, and aggression, are commonly seen in severely affected patients and our patient had history of seizures but other behavioral problems and mental retardation were absent.

Nodular thickening of the valves and deposition of GAGs in the myocardium leads to valvular disease, biventricular hypertrophy and heart failure [5]. The skin of these patients is inelastic and thickened with distinctive ivory-white papules of 2 to 10 mm in diameter [8].

Oral manifestation include peg shaped, hypoplastic, carious teeth with abscesses, dentigerous cysts with delayed eruption particularly with first permanent molars [11], and gingival tissue will be hyperplastic and hypertrophic [11].

Radiographic features of Hunter syndrome are unusual thickness of all bones, and irregular epiphyseal ossification in the joints of the hand, shoulder, and elbow. The hands tend to have a claw-like appearance. Ribs will be thickened with unusual shape, and clavicles will be increased in bulk. The lateral surfaces of the vertebral bodies are notched in appearance. Restricted joint mobility due to skeletal changes is seen. Characteristic features of extremities are shortening of the long bones, narrow epiphyses, irregular metaphyses and proximal pointing of metacarpals and metatarsals. There will be contractures developing secondary to GAG deposition in tendons [9]. J-shaped sella turcica and a thickened skull are the cranial system manifestations. Odontoid dysplasia and anterior beaking of the lower thoracic and upper lumbar vertebral bodies are seen resulting in focal kyphosis [9]. All these radiographic features were observed in the present case.

Usually Hunters syndrome is suspected based on the facial features. Analysis of urine GAG levels can be used to confirm MPS. Presence of excess dermatan sulfate and heparan sulfate in urine lead to diagnosis of MPS I, MPS II, or MPS VII [9].

Enzyme analysis is diagnostic for particular type of MPS. Enzyme assay is done on cultured fibroblasts, leukocytes, plasma, or serum. In males when I2S is absent or low is considered to be diagnostic of Hunter syndrome. Enzyme activity assays may be done on cells that are cultured from amniotic fluid or in chorionic villus biopsy tissue [12], and even in fetal blood. Prenatal diagnosis can be done by using molecular analysis if the family specific mutation is recognized [13].

Management of Hunter syndrome has been palliative and mostly focused on the treatment of signs and symptoms. Various approaches have been tried to replace the missing enzymes in Hunters syndrome. They include bone marrow transplantation, fibroblast transplantation, human amnion membrane implantation, white blood cell infusions, serum or plasma infusion gene therapy, intraperitoneal implantation of myoblasts overexpressing I2S, and enzyme replacement therapy [1]. Because of the valvular dysfunction, prophylactic antibiotic therapy is compulsory before any surgery or major dental procedure [13].

It was shown that in children when transplantation is done, skin changes, cardiovascular complications and hepatomegaly are reversed but skeletal changes are irreversible [6]. Decompressive surgery is used to prevent neurologic damage due to spinal cord compression [9]. Orthopedic surgery, physiotherapy and daily exercise may improve mobility of joints.

Standard dental care is advised in patients of Hunters syndrome with follow up of every 6 months. Routine procedures may be sometimes difficult due to reduced mouth opening and certain patients may require general anesthesia, which is a risky procedure in Hunters syndrome [14].

CONCLUSION

MPS represents a multisystem disorder which presents with numerous clinical manifestations affecting most of the organs. Thorough examination and evaluation is required to classify the disorder into the exact type. In the present case, history and prudent physical examination along with appropriate radiological investigations helped us in diagnosis. Evaluation of the patient revealed that patient belongs to mild form of Hunters syndrome. Our case had strong family history, typical clinical features, radiographic manifestations which help us to come into conclusion of a MPS even before GAG analysis. Enzyme assay can be studied for the further confirmation of the disease. Regular dental care is advised with proper follow up.

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