

## MUCOPOLYSACCHARIDOSIS TYPE-II: A RARE CASE OF HUNTER SYNDROME

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### Article Info

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### Abstract

Mucopolysaccharidoses (MPS) are rare genetic diseases lysosomal storage disorders, in which there is deficiency of certain specific lysosomal enzymes involved in the glycosaminoglycan (GAG) breakdown pathway. Hunter syndrome is type 2 MPS caused by a deficiency of the lysosomal enzyme iduronate-2-sulfatase. It is a rare genetic syndrome of x linked recessive inheritance with a prevalence of 1:100,000 births. It is a heterogeneous disease with multisystem involvement including skeletal, joint, airway, cardiac, and hearing and vision impairment with mild to severe mental retardation. Treatment option includes haematopoietic stem cell transplantation and recombinant i.v. enzyme replacement therapy, here we discussed a case of hunter syndrome that presented in our hospital with typical features of hunter syndrome, and was diagnosed with specific enzyme assay.

**Key-words:** Mucopolysaccharides, Glycosaminoglycan, Dysostosis multiplex

**Key Messages:** Given the clinical heterogeneity and rarity of MPS, clinician should be aware of this syndrome and newborn screening may be the key to identifying individuals before the onset of irreversible clinical disease. In the interim, greater physician awareness of the MPS disorders will enable early, accurate diagnosis and treatment and improve patient outcomes.

**Introduction:**

Lysosomal storage disorders are characterized by the dysfunction of the lysosomal enzymes. Defect in catabolism of glycosaminoglycans (GAGs) due to a genetic mutation and GAG accumulation in the tissues comes under mucopolysacchridoses (1). The pathogenesis involves accumulation of undegraded or partially degraded substrates inside lysosomes as well as in the extracellular compartment. MPS is a rare entity with a total incidence of 1/2000 live births (2). MPS-II (Hunter disease) is one of the rare types of MPS with typical manifestation such as coarse facies, visceromegaly, hernia, short stature, dysostosis multiplex with joint contractures, clear corneas, mild/no mental deficiency (3). urinary GAG measurements are usually first investigation to be done in patients with characteristic features followed by specific lysosomal enzyme activity in leukocytes for definitive diagnosis (4). Today, therapeutic options are few in form of enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation in MPS (5-7). Here we discussed a case who presented in our opd with typical features of hunter disease. Urinary GAG measurement suggestive of MPS followed by lysosomal enzyme which confirmed the diagnosis of Hunter disease.

**Case History** - Parents of a 14 years old male child came to us with concern of not gaining height for last 6 years. Parents also noticed that child developed progressive bilateral flexion deformities of fingers and elbow for last 3 years such that he was unable to make fist, perform fine motor tasks and due to development of bilateral knock knee, was unable to run fast for last 2 years. He was born of nonconsanguineous marriage, full term normal delivery, cried

immediately after birth. No feeding difficulties, any h/o jaundice, lactose intolerance. Developmental milestones were normal along with normal scholastic performance, social, family and peer interaction. No behavioural problems were there. Anthropometry: Height (108 cm) was less than 3rd percentile with disproportionate short stature (US/LS: 1.098), MPH was 165.5cm. Tanner's Score was done (A1P1TV=5ml) which came to be normal. Stretched penile length was 3.8cm. Excessive hair growth was present all over the body (figure1). Other than that, typical coarse facies with frontal bossing, low set ear (figure 2), Broad wrist & short carpals & metacarpals were also present. On further evaluation flexion deformities in B/L elbows (figure 3), fingers, B/L knock knees were also there. Patient was investigated for short stature. Primary investigations were normal in form of normal blood count, liver function test, renal function test and normal routine urine microscopy. Serum glucose (85/dl), S. Alkaline Phosphatase (252IU/L), S. Ionic Calcium (1.13mmol/l) and thyroid function test (TSH: 1.8 $\mu$ IU/ml, T4: 8.82  $\mu$ g/dl, T3: 1.23 ng/ml) also came to be in normal limit. Basal fasting S. Cortisol (6.2ug/dl) and S.Prolactin (4.25ng/ml) were within range, CXR-PA view showed bilateral wide ribs . X-Ray left wrist (AP view) showed bullet shaped metacarpals along with hypoplastic distal ulna and radius hypoplastic and irregularly shaped carpal bones (figure 4). X-Ray skull (Lateral view) depicted expanded diploe with frontal bossing (figure 5). All these skeletal findings were suggestive of Dysostosis multiplex. Keeping in mind provisional diagnosis of mucopolysaccharidosis, urine screening for glycosaminoglycans (GAG) was done which came out to be positive. Ophthalmological examination confirmed no corneal clouding or

retinal degeneration. Ultrasound abdomen had massive hepatomegaly. Audiometry test and MRI brain was normal. Furthermore, the diagnosis was confirmed by enzyme assay which came out to be due to iduronate sulfatase deficiency. Patient was referred to higher centre for enzyme replacement therapy due to non-availability in our centre and nonaffordability of patient.



**Figure 3- bilateral elbow and wrist flexion deformity**



**Figure 1- excessive hair growth over body**



**Figure 4- hypoplastic bullet shaped metacarpels and hypoplastic radius and ulna**



**Figure 2- typical frontal bossing coarse facial features.**



**Figure 5- x ray skull lateral view with expanded diploe and frontal bossing**

**Discussion:**

Inborn error of metabolism is a group of disorders in which mucopolysaccharidoses is an important entity in which there is a defect of glycosaminoglycan (GAG) catabolism due to deficiency of certain lysosomal enzymes. Pathogenesis involves accumulation of GAG in various organs and tissues of patients affected by MPS which affect various systems of body causing it a multisystem affecting disease. Charles, a Canadian physician was the first who described mucopolysaccharidoses in patient.

Hunter syndrome is type 2 Mucopolysaccharidosis which is caused by a deficiency of iduronate-2-sulfatase enzyme. Hunter syndrome runs in x linked manner as opposed to all other mucopolysaccharidoses which inherited as autosomal recessive manner that is why it affects males exclusively though few cases of female child has been documented also (10). Hunter syndrome has been divided into two subtypes on the basis of severity of symptoms. In subtype A patient presents early in life mostly in first year of age with severe mental retardation and slow neurological development. Life span is short and most common cause of death is upper airway obstruction and cardiovascular involvement in adolescence age group (8). subtype B is somewhat milder form in which there may be mild mental retardation but intelligence is usually normal and death does not occur until adulthood. Our patient presented with near normal intelligence at the age of 14 years so we categorized him in subtype B that is in milder form. Common features of hunter syndrome are coarse facial features, macrocephaly, broad nose, prominent supraorbital ridge, large tongue, joint stiffness and contracture as seen in our patient. Ocular features constitute of Retinopathy and optic nerve atrophy which was not there in our case.

Conductive and sensorineural hearing loss are other features of hunter syndrome which were also absent in our case. Usual cause of death in hunter syndrome is upper airway obstruction (12). Tracheal or bronchial wall weakening, stiffness of the chest wall, and abdominal distention are main contributing factors of airway obstruction.

Urinary GAG concentration determination is the screening test to do on strong clinical grounds of MPS which usually are very elevated in patients of MPS (three or more times) compared to normal levels. Presence of excess dermatan sulfate and heparan sulfate in urine lead to diagnosis of MPS II. Confirmation of specific type of MPS is done by Enzyme analysis which is done on cultured fibroblasts, leukocytes, plasma, or serum. In males when iduronate-2-sulfatase is absent or low is considered to be diagnostic of Hunter syndrome. Since hunter syndrome is a multisystem disease and management of Hunter syndrome has been palliative therefore it is 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 iduronate-2-sulfatase, and enzyme replacement therapy.

**Conclusion:**

Hunter syndrome is a rare disorder of various outcomes ranging from mild intelligence impairment to rapidly progressive disease with fatal outcome. It involves multisystem of body with typical features of MPS. Diagnostic confirmation can only be done by specific enzyme assay. Therefore, it is necessary to take

multidisciplinary approach to diagnose and thereafter to treat this disease.

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