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CASE REPORT

HUNTER SYNDROME: A RARE CASE OF MUCOPOLYSACCHARIDOSIS

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Abstract :
Mucopolysaccharidosis(MPS) is an inherited lysosomal storage disease.It constitutes a group of heterogeneous disorder occurs due to complete or partial absence of enzymes that breakdown the mucopolysaccharides into simpler forms.This deficiency results in accumulation of undegraded glycosaminoglycans (GAGs) into different organs of body causing syndrome manifestation. Here we present a very rare case of MPS type II(Hunter Syndrome) with some atypical pictures such as milder form of mental retardation with normal intelligence, no evidence of corneal clouding, genu valgum and an oxycephaly head. Other clinical features are usual of MPS which was initially confused with common occurring achondroplasia and congenital hypothyroidism, but skeletal survey clearly diagnosed this case as MPS especially by spine and hand x-rays.

Key Words: Hunter Syndrome, Mucopolysaccharidosis (MPS) type II, Skeletal Changes.

INTRODUCTION

MPS is an inherited storage disease caused by the deficiency of the lysosomal enzymes which metabolizes the complex molecules called GAGs(previously called mucopolysaccharides).They are complex long chain carbohydrates in different cells of body like bones, cartilages, tendons, cornea, skin and connective tissues and help in growth of organs and systems. Deficiency of specific enzymes lead to accumulation of undegraded GAGs in different parenchymal, mesenchymal tissues and also storage within neural cells, and abnormal excretion of GAGs products like heparan sulfate, keratan sulfate, chondroitin sulfate and dermatan sulfate in urine[1,2].

Since they are very toxic and result in progressive but permanent damage of cells.These damage lead to abnormal body growth and affect the appearance, physical activity, organs and systems functioning and in most cases mental development as well.

All MPS are group of autosomal recessive disorder except Hunter syndrome which is X-linked recessive mainly in males, however few cases have been reported in female

patients[3].Common clinical presentation are coarse facials, corneal clouding, mental retardation, stunted growth with antero-inferior beaking of vertebral bodies, macrocephaly and J-shaped sell-turcica on skeletal analysis.The skeletal abnormalities collectively called as Dysostosis Multiplex(by Hurler in 1931)[4].We are here describing a case of MPS type II(Hunter syndrome) because of its rarity and atypical features of no corneal clouding, mild mental subnormality, severely stunted, genu-valgum and an oxycephalic head presented at 8-years of age.The purpose of presenting this case is rarity of this disorder, to highlight the distinctive features of Hunter syndrome(MPS-II) and how radiological analysis is definitive to diagnosed it accurately even if enzymatic and urinary test kits are not available.

CASE REPORT:

A eight years old boy presented to the paediatric out-patients department for his recurrent upper respiratory tract infection and low grade fever for last 3-years.The patient's parent was concerned about his gradual and progressive abdominal protuberance for last 6-years duration and thick lips.There was no history of weight loss.no abnormal bowel behaviour like constipation or diarrhea; no evidence of seizure or loss of consciousness.He was school going child for last 2-years but not good in his study.

On clinical examination,he was short stature measuring 99 cm in height with average build.His skull was large and conical in shape with short neck.Facial features showed coarse and thick hairs over scalp and eye-brows.The nasal bone was depressed with prominent nasal alas and mucoid running nose.The lips were thick, bulky and protruded outward. Examination of oral cavity showed mal-aligned teeth, enlarged adenoid and thick tongue. On ocular examination no evidence of corneal clouding and fundus of eye-ball was normal.The auditory functions were normal. The abdomen was distended but no hernia noted around umbilicus or inguinal regions. His liver and spleen were enlarged and also evident on ultrasonography measuring 16 cm and 15 cm respectively. Cardiological examination was normal. His upper limb as well as lower limb were short with elevated and widely apart scapulae. The hands were short and stubby with semi-flexion at distal interphalangeal joints. Lower extremities showed outward deviation of legs at knee joints(genu-valgum).

On the basis of clinical examination, he was suspected as a case of achondroplasia or congenital hypothyroidism but no one suspected of MPS.

His blood thyroid assay was within normal limits. Suspecting a case of achondroplasia and hypothyroidism, skeletal survey was advised and referred to radiology department.

His skull x-rays showed an enlarged and deep J-shape sell-turcica. The bones of skull and sutures were normal. Chest x-ray showed paddle/spatula shape ribs that is narrow at vertebral ends and wider at sternal end. The clavicle was short and thickened. The glenoid cavity shallow. Antero-posterior and lateral x-rays of dorso-lumbar spine depicting well defined antero-inferior beaking of vertebral bodies. Convexity of superior and inferior surfaces of vertebral bodies.Spinal curvature showed marked kyphosis at lumbar region.

The lower end of radius and ulna were angulated towards each other with dysplastic cupped and flared metaphyses. Only two carpal bones visualized suggesting developmental delay of bones. Metacarpal bones were short with expanded medullary cavities and thinned cortices

forming convex shape. The metacarpals showed proximal end tapering.The proximal phalanges of both hands were looking like a bullet that is proximally widened than distal ends and semi-flexion deformity at distal interphalangeal joints.

The hip joints having shallow acetabular cavities. The femoral heads were underdeveloped and associated with coxa-valga. The iliac bones were small and hypoplastic.The knee joints showed fragmented epiphyses of tibia and genu-valgum deformity.

Thus these skeletal features are very characteristic of MPS especially proximal tapering of metacarpal bones,bullet like proximal phalanges, antero-inferior beaking of vertebral bodies and lumbar kyphosis. These findings nagets the diagnosis of achondroplasia and congenital hypothyroidism and established a case of MPS.

The skeletal findings were quite characteristic of MPS, we made a final diagnosis of Hunter syndrome on the basis of his history, clinical features and radiological assay particularly due to absence of corneal clouding ,normal intelligence.

Since rarity of occurrence of disorder and unavailability of proper test kits,we could not able to access the 24-hours urinary level of GAGs and also enzyme evaluation either.

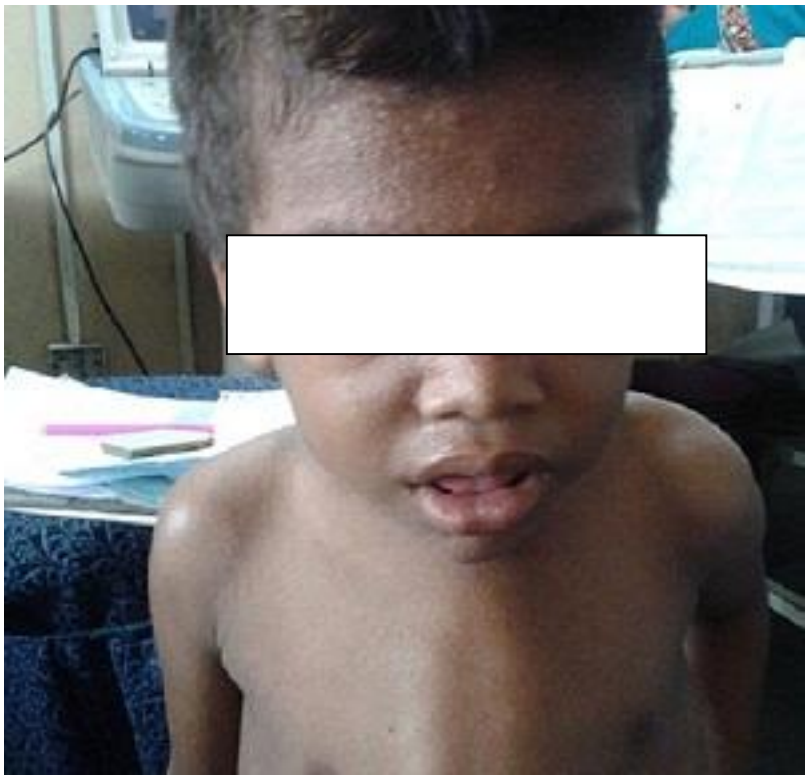

Fig:1-Boy with Mucopolysaccharidosis showing coarse facial features like,depressed nose,coarse hair,epicanthus,flared nostril,thick tongue with protrude lips but no corneal cloudings.

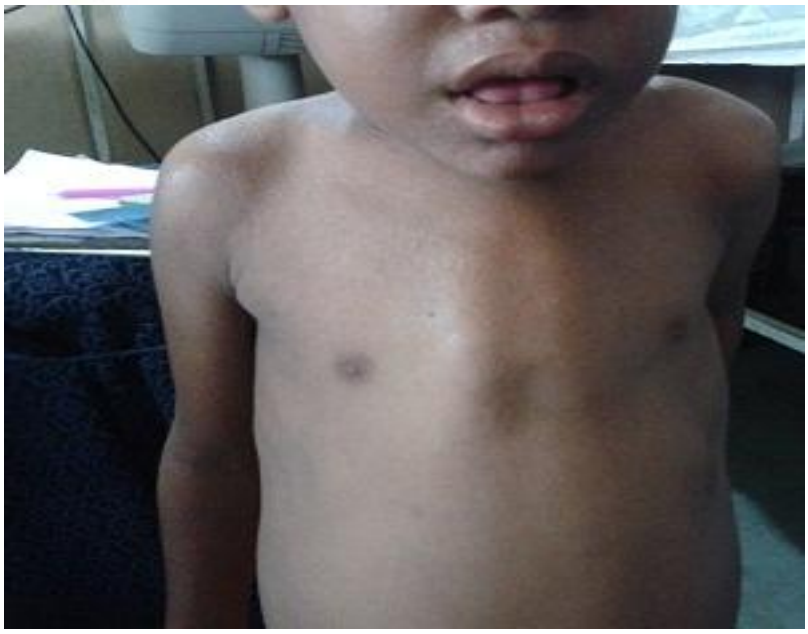

Fig:2-Boy with Mucopolysaccharidosis showing short neck,forward protruded sternum(pectus carinatum) and distended abdomen.

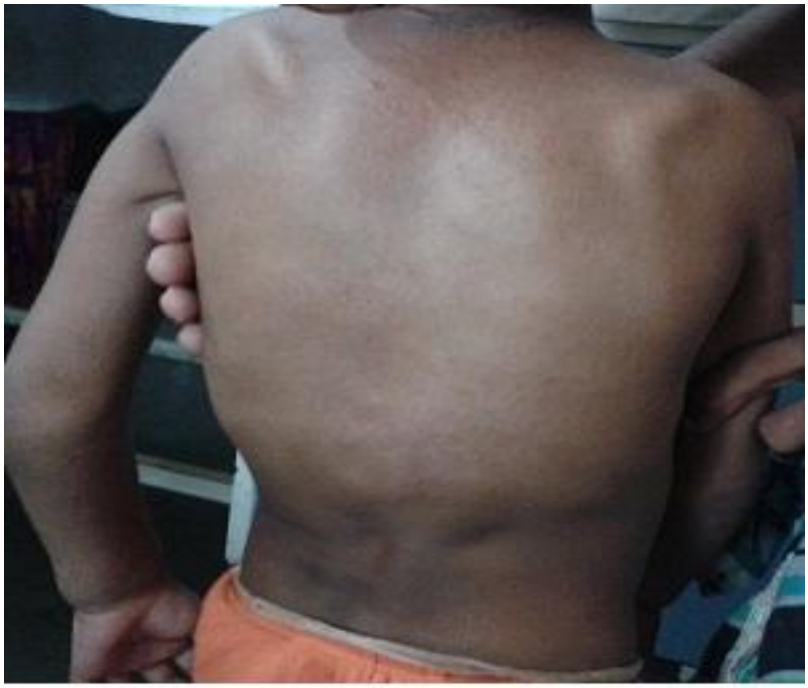

Fig:3-Image showing widely apart scapulae with rounded borders,and significant lumbar kyphosis.

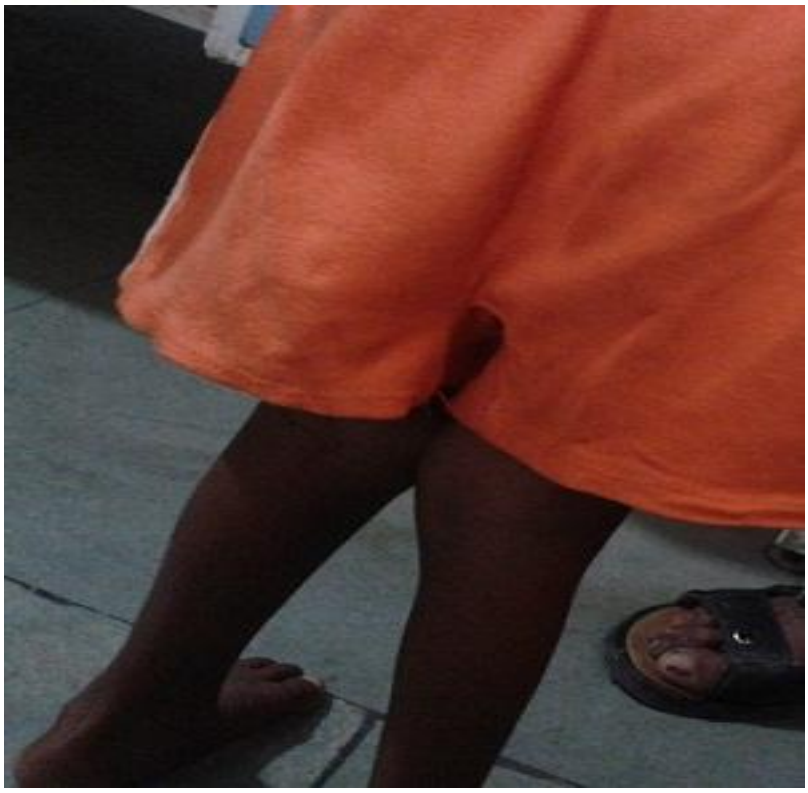

Fig:4-Picture showing genu vulgum in a boy with mucopolysaccharidosis.

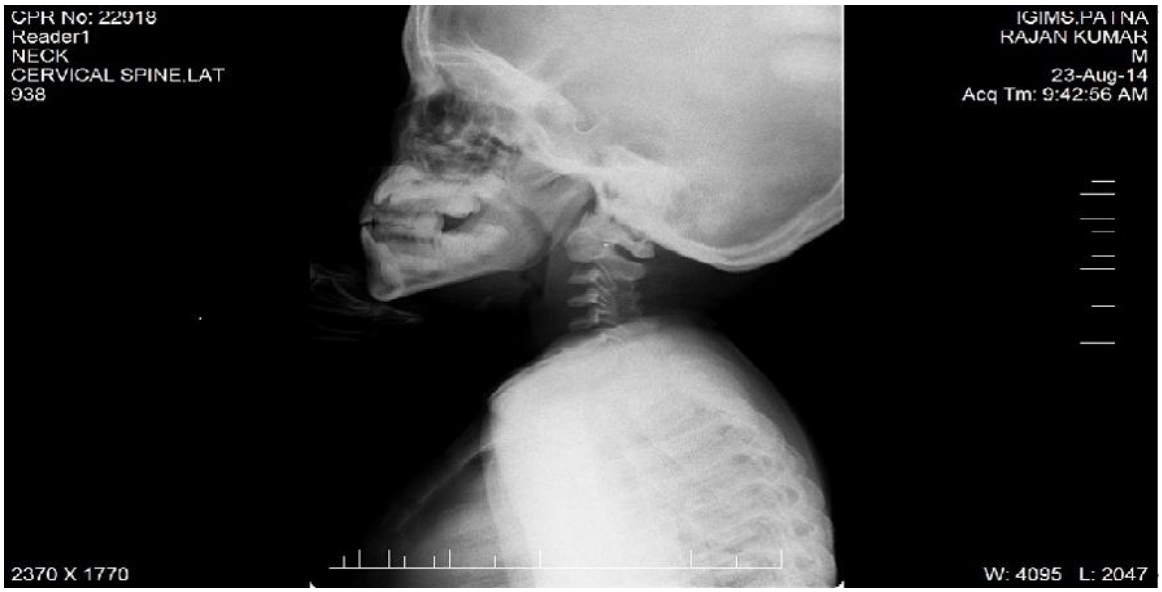

Fig:5-X-ray skull showing enlarged skull size,hypoplastic and small facial bones with J-Shaped sella-turcica.

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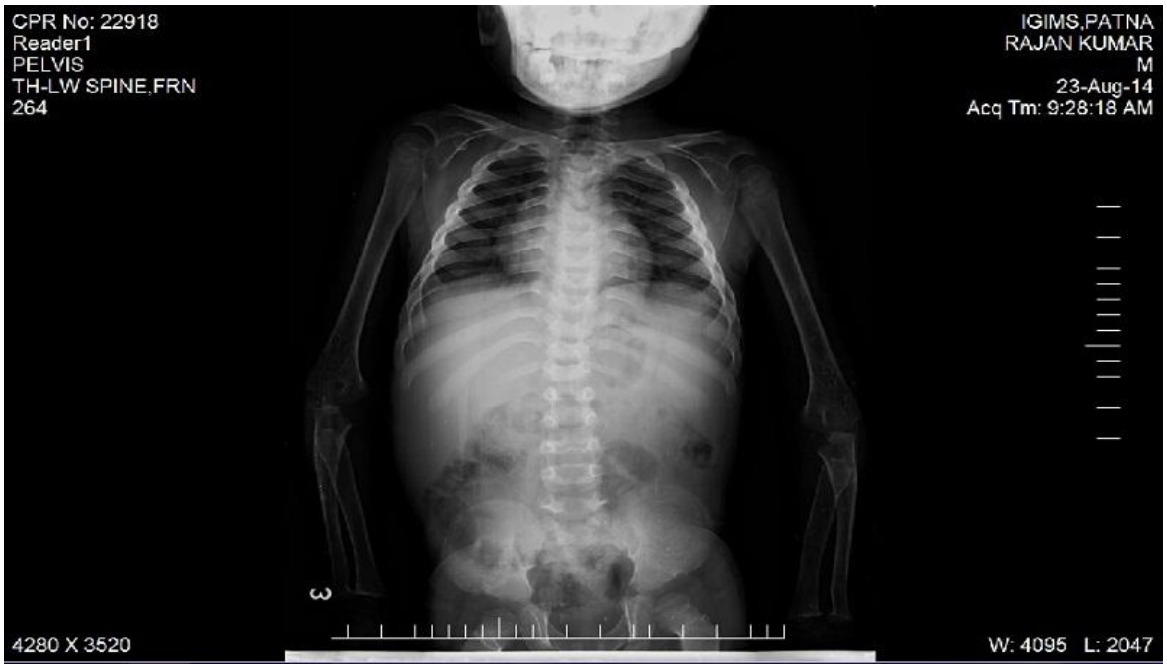

Fig:6-X-ray showing narrow thoracic inlate,thick medial part of clavicle,shallow or ill developed glenoid cavities and abnormal constriction around anatomical neck.There is also narrow pelvic brim,flared ilial wings,shallow horizontal acetabulum.

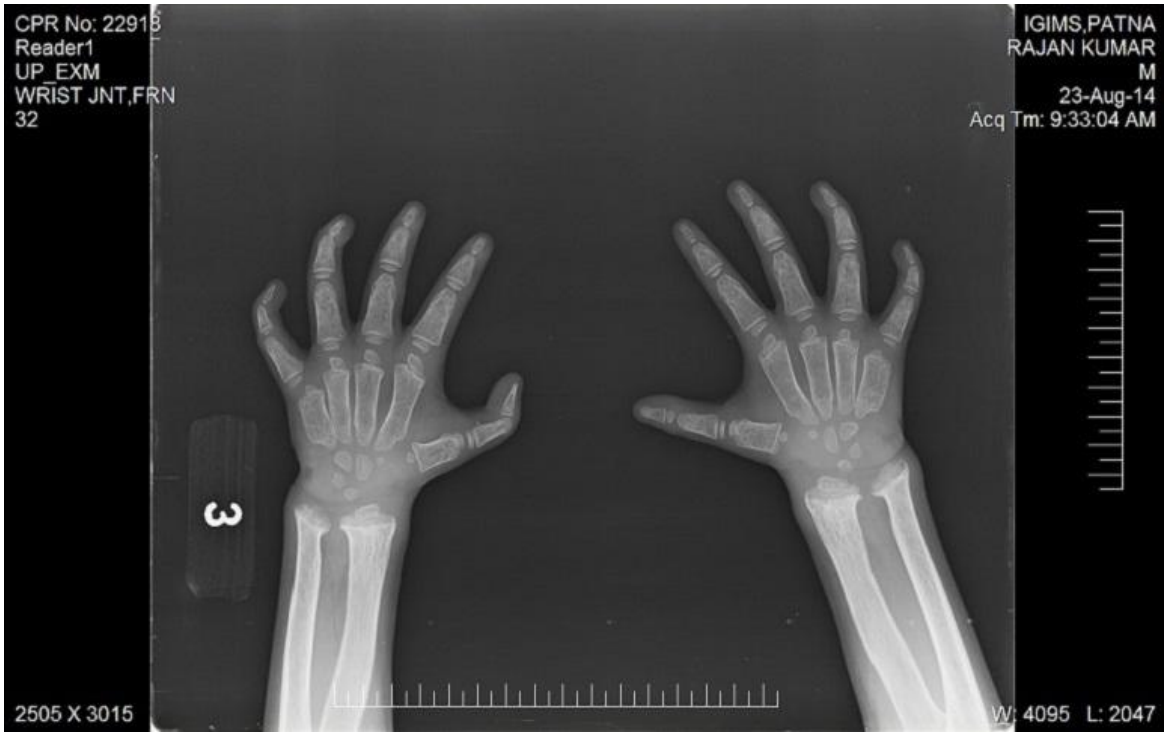

Fig:7-X-ray hands showing proximal tapering of metacarpals,bullet shaped proximal phalanges at distal ends with dysplastic and angulated distal ends of radius and ulna.

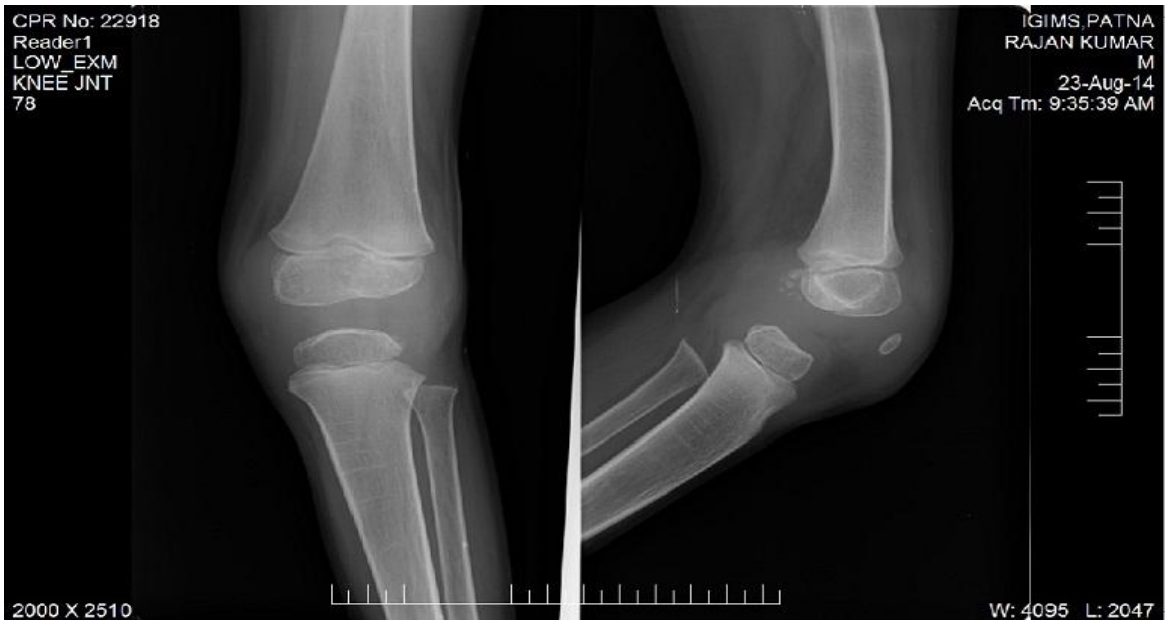

Fig:8-X-ray knee joint showing dysplastic epiphysio-metaphyses of tubular bone with focal fragmented change in femoral epiphyses.

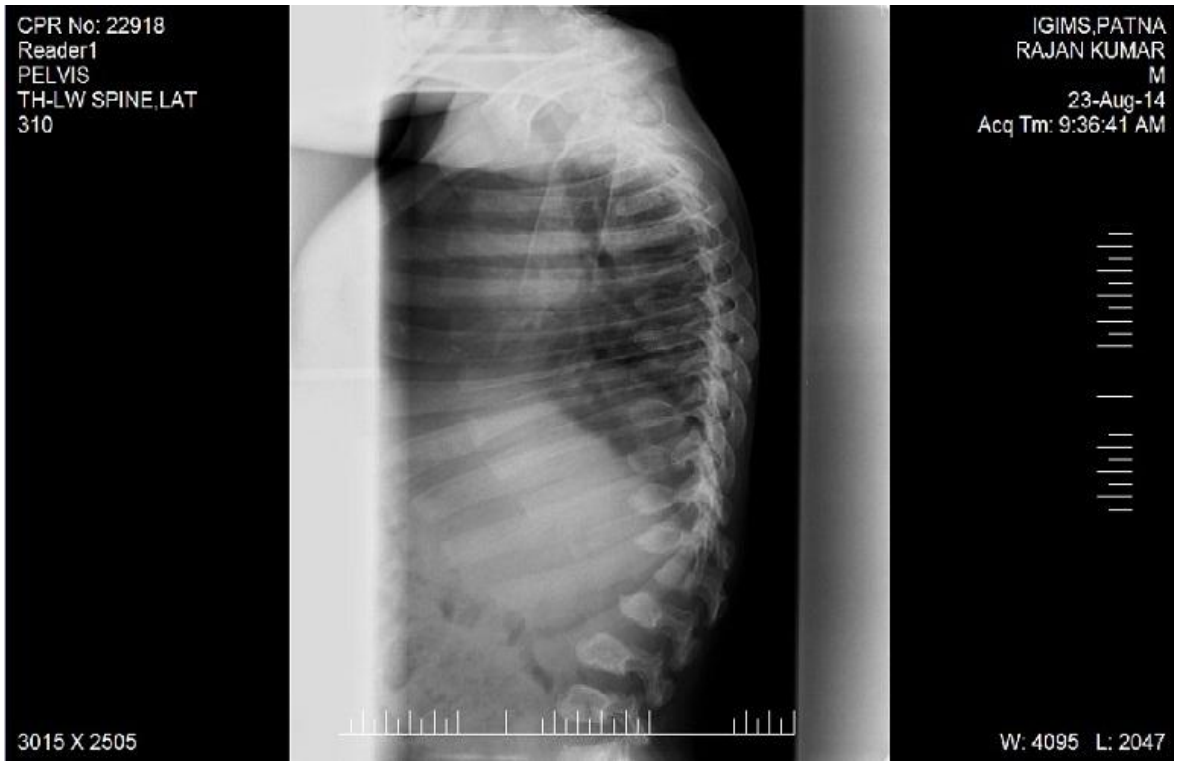

Fig:9-X-ray of thoracolumbar spine showing typical antero-inferior beaking of vertebral bodies and severe kyphosis at lumbar region.

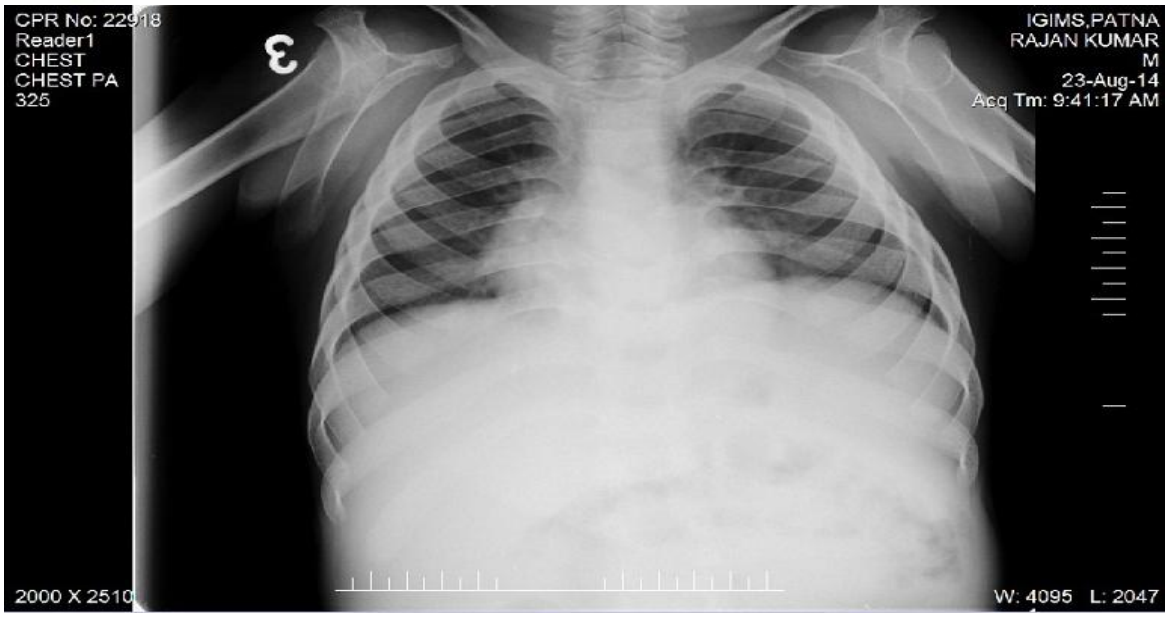

Fig:10-X-ray chest showing typical paddal/spatulated shape ribs(narrow vertebral ends and wider sternal ends).

DISCUSSION:

Hunter syndrome is a form of Mucopolysaccharidosis(MPS).MPS is heterogeneous group of hereditary disease secondary to deficiency of specific lysosomal enzymes leading to an excessive accumulation of GAGs. Almost every cell of body are involved in MPS.This disorder is marked by the urinary excretion of GAGs products like heparan sulfate, keratan sulfate,chondroitin sulfate and dermatan sulfate[1,2].

It was Charls Hunter(1917) who first described MPS,a rare disease in two Canadian brothers[5,6].

Mucopolysaccharide also called Glycosaminoglycans(GAGs) are the major part of intercellure connective tissues.Due to lack of enzymatic activity defective or undegraded mucopolysaccharides start accumulating into different tissues and organs like chondrocytes,osteocytes and cells of tendons,fascia,blood vessel wall,cardiac valves,meninges,cornea etc.Abnormal mucopolysaccharides seen in reticuloendothelial systems of body and also in the epithelial cells of kidney and various endocrine organs[4].

Several distinctive types of MPS have been described,each with distinctive clinical and radiological features.Hurler and Morquio syndrome are most well known radiologically while Hunter and other types are very rare.The main clinical features of MPS are coarse facial changes,corneal clouding,stunted growth and mental retardation.

All MPS are autosomal recessive except Hunter syndrome which is X-linked recessive and very rare in general population.MPS type II is caused by partial to complete lake of enzyme Iduronate-2-Sulfatase by Neufeld in 1987[7].The cause of hunter syndrome is

a mutation in a gene which codes and controls the production of the enzyme Iduronate-2-sulfatase.This gene, known as IDS(locus mim no.300823), is located on the long arm of the X chromosome [Xq27-28][8].Its prevalence of 1 in 1,40,000 to 1,56,000 males live birth[9].Hunter syndrome is mostly seen in males however few cases have been reported in females[3].This can occur in any ethnic group but slightly more incidence noted in the Jewish population living in Israel.

Hunter syndrome is divided into two types(type A and Type B) on the basis of age of survival and the presence or absence of central nervous system disorder.Type A is the severe form usually diagnosed in children around 18-36 months of life and considered as classic form of syndrome.Children with type A may survive upto the 2nd to 3rd decade of age.Type B is much milder than type A and may not be diagnosed until adulthood.Individual with type B may survive upto their age of 70s.Type B's physical appearance are very much to those in type A but the severity of central nervous disease is very high along with more skeletal changes in type A.Milder form(type B) is compatible with survival and can lead to family life[10].Type A hunter syndrome is very similar to Hurler syndrome but symptoms progresses very fast and becomes worse in case of Hunter.No such biochemical markers that distinguish the two forms of the syndrome; it is the clinical presentation that determines severity. It is hoped that in the future it will be possible to link specific molecular genetic anomalies to clinical manifestations, thereby enabling a reliable prognosis in each individual case.

The common clinical pictures of MPS type II are macrocephaly,short stature,mental subnormality,coarse facial changes,protuberant belly,depressed nose,large tongue and jaws.After three to four years of life the classical features start to appearing, as with our case the boy presented at 8-years of age with some atypical clinical features.

Liver and spleen enlargement are common,heart disease and recurrent respiratory tract infections are major concern as they are leading cause of death in these disorder.Corneal clouding with visual impairment,auditory disfunctions and umbilical to inguinal hernias are very common occurrence.In our case patient having significant recurrent respiratory tract infection with mild to moderate hepatosplenomegaly but atypically did not show corneal clouding,poor vision,hearing defect or any cardiac abnormality.In MPS type II central neurological signs and mental retardation are common and progressive,but in our patient there is mental retardation but in milder form with normal intelligence however no neurological signs noted.Skeletal survey characteristically showing our case as Mucopolysaccharidosis and clinically it is classified as Hunter syndrome.Skeletal changes are due to dysplastic growth of epiphyses and metaphyses,defect in modeling and remodeling of bones.Deformed J-shape sell-turcica is caused by infiltration of GAGs products in meninges forming subarachnoid tiny cysts depresses the sella**[4]**.

Confirmatory diagnosis is done by urine glycosaminoglycan variants (chondroitin sulfate B and heparan sulfate)[11], enzyme assay in cultured skin fibroblast,blood and plasma samples using substrate specific for I2S.Absent or low activity of I2S in male is diagnostic of Hunter syndrome.If facilities available gene mapping for IDS(located on X-chromosome, Xq27-28, mim no.300823) quite completely resolve the diagnosis.Management includes medical care directed towards relieving the various symptoms.Treatment with Elaprase replaces Iduronate Sulfatase in body and helps in reducing symptoms especially by increasing functional

capacity of muscles, joints, lungs, liver, and spleen volume and urine GAGs excretion[12]. Hematopoietic stem cell transplantation, used for treating a number of enzyme deficiency disorders (like Hurler syndrome), has not proven effective in halting the progression of Hunter syndrome[13].Gene therapy using a retroviral vector may offer future hope of definitive treatment.

CONCLUSION:

MPS is a group of disorder occurs due to deficiency of specific lysosomal enzymes causing multiorgan multisystem abnormality.Almost every cells of the body affected and produces varied but characteristic clinical pictures and skeletal deformities(Dysostosis multiplex) which are quite sufficient to diagnose a case of MPS.Thus careful skeletal analysis and clinical approach can accurately diagnose the exact type even if enzymatic and urinary test kits are not available as in most centers of developing countries.

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