ORIGINAL RESEARCH PAPER

Biochemistry

A CASE REPORT ON CLINICAL MANIFESTATIONS , BIOCHEMICAL AND MOLECULAR ANALYSIS OF MUCOPOLYSACCHARIDOSIS TYPE 1 (HURLER-SCHEIE SYNDROME) PRESENTED TO A TERTIARY CARE HOSPITAL.

KEY WORDS:

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ABSTRACT

OBJECTIVES: To emphasize the presentation, biochemical and molecular analysis of mucopolysaccharidosis type-1,presented to a tertiary care hospital.

RESULT: The patient was diagnosed with Type-1 mucopolysaccharidosis with a homozygous nonsense mutation in exon xiv of IDUA gene.

CONCLUSION: Primary care providers and pediatricians must increase their awareness of MPS I-H, to better recognize the peculiar signs and symptoms and promptly refer the child for futher Biochemical screening and Molecular diagnostics.

INTRODUCTION:

Mucopolysaccharidoses (MPS) are a group of rare,autosomal recessive,hereditary disorders of Glycosaminoglycans (GAGs) metabolism that are clinically progressive and characterized by intralysosomal accumulation of GAGs in various tissues due to deficit in lysosomal acid hydrolases. GAGs are unbranched polyanionic,polysaccharides of disaccharide repeats,each repeat unit comprising an acid sugar linked to a glycosamine. Seven distinct clinical types and numerous subtypes of mucopolysaccharidoses have been identified. MPS Type-1 (Hurler-Scheie syndrome) is a rare autosomal recessive disorder caused by the deficiency of lysosomal enzyme α1-iduronidase(IDUA) having prevalence of 1 in 1,00,000 **(1)**.There are very few cases of Hurler syndrome reported in India. This is a case of a 7 year old child, presented to our tertiary care hospital with coarse facial features and multiple skeletal abnormalities,screened and diagnosed as Hurler syndrome.Through this case report we are highlighting the important clinical manifestations, radiological findings, biochemical approach and molecular analysis of such rare disorder.

Case Presentation:

A 7year old boy born from 3rd degree consanguineous marriage,first in order, presented to our paediatric opd with chief complaints of cough and cold since 1 week. He has a past history of recurrent rhinitis since past 2 years,subsiding on taking medications.On examination the child has coarse facial features including frontal bossing,flat nasal bridge and short stature associated with widened chest, umbilical hernia , genu valgum and multiple skeletal deformities(fig.1) .No history of similar presentations in the family. Based on the above presentation, the child was referred for radiological and blood investigations.Ultrasound abdomen confirmed grade-II hepatomegaly along with splenomegaly. X-ray studies showing multiple radiological abnormalities like J-shaped sella tursica(fig.2), widening of phalanges and metacarpals with proximal tapering (fig.3).

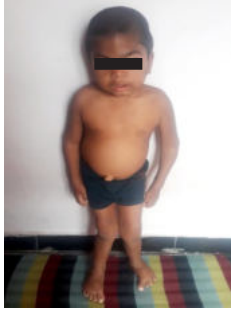

Figure 1- The 7yr old boy, showing multiple skeletal deformities like coarse facial features,frontal bossing, umbilical hernia, genu valgum etc.

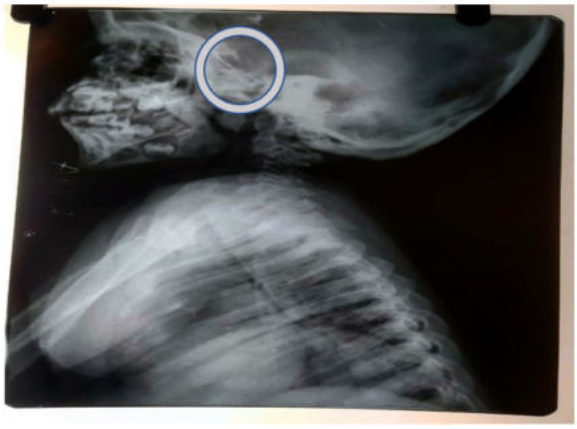

Figure 2- X-ray skull, lateral view, showing J shaped Sella Turcica

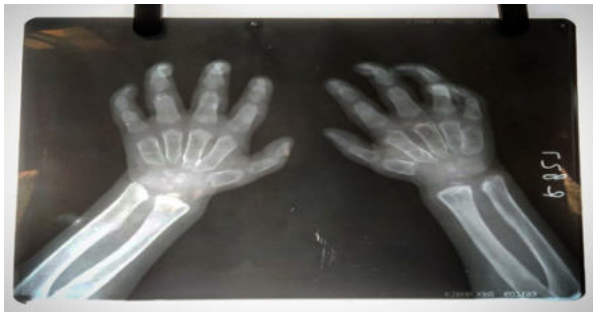

Figure 3-Xray hands showing widening of phalanges and metacarpals with proximal tapering, bullet shaped phalanges.

Due to these specific clinical and radiological findings the patient was suspected for Mucopolysaccharidoses and was referred for further biochemical screening.

Urine for MPS was performed and based on positive C-TAB test results (as shown in Table.1) ,the child was referred to higher center for further biochemical and genetic analysis.Leucocyte enzyme analysis was performed by artificial fluorogenic substrate method , which diagnosed

reduced activity of iduronidase(IDUA)*i.e* ***0.8 nml/hr/mg****(Normal range:20-108 nml/hr/mg*) and normal levels of β-galactosidase **134 nml/hr/mg**(Normal range:70-324 nml/hr/mg) in leukocytes.

Based on the above investigations, the samples were further sent for IDUA gene analysis. All the 14 exons of α-L-Iduronidase(IDUA) gene (flanking exon/intron regions),were amplified by PCR and checked for any mutations. A known homozygous nonsense mutation at 628 position(stop codon), in Exon XIV of IDUA gene was detected, confirming the diagnosis.

Table 1- Various urine tests performed to diagnose inborn metabolic errors.

TEST	RESULT	INFERENCE
Di-NitroPhenylHydrazine	No orange Turbidity found	Negative for phenylketonuria.
10% FeCl3	No blue/green color formed.	Negative for phenylketonuria.
Brand's	No cherry red color formed.	Negative for cysteinuria.
Cetyl Trimethyl ammonium bromide	Appearance of turbidity within 20mins	Positive for MPS.

DISCUSSION:

The absence of the enzyme α-L-iduronidase leads to accumulation of GAGs like heparan sulphate and dermatan sulphate in lysosomes of various tissues of the body.Such accumulations causes various clinical manifestations in a case of hurlers like, shortstature, skeletal malformations like widened phalanges and metacarpals, frontal bossing and genu valgum. The other manifestations include organo megaly, mental retardation and umbilical hernia**(2)**.Urine Cetyl Trimethyl ammonium bromide (C-TAB) test is the most important qualitative test for screening of MPS. Most MPS patients have higher excreation of glycosaminoglycans in urine ,compared with age matched normal subjects.GAG excretion can also vary depending on the severity of the disease phenotype,even within the single subtype of MPS**(3)**. Thus, an accurate diagnosis requires more specific tests . Hence, once screened positive for GAGs in urine, the patient can be subjected to further specific tests like leucocyte , fibroblast enzyme assay and IDUA gene analysis. Leucocyte cultured lymphoblasts, or fibroblasts are generally used, with the actual choice depending upon the characteristics of the enzyme to be assessed as well as the corresponding method of detection**(4)**. The fluorogenic (4-methylumbelliferyl) , method was used in this case to detect the enzyme activity in leucocytes. The gene encoding α-L-iduronidase,located on chromosome 4p16.3 contains 14 exons encoding for a polypeptide of 653 amino acids**(5).** In this case, all the 14 exons of IDUA gene were amplified and subjected for the screening for any mutations. A known homozygous nonsense mutation at 628 position(stop codon), in Exon XIV of IDUA gene was detected following the PCR. After the diagnosis of the type of MPS and its specific mutation,carrier testing and prenatal testing of the siblings can be performed. The use of Molecular testing as an initial screening is limited due to the extreme genetic heterogeneity ,that characterizes all types of MPS**(3).**

Early diagnosis is the key in the prompt treatment of such cases of inborn metabolic errors. Most of the children with hurlers appears normal in initial stages, but if left untreated the disease can be progressive and may lead to several complications. Allogeneic hematopoietic stem cell transplantation (HSCT) along with Enzyme replacement therapy (ERT) with human recombinant laronidase(peri-transplantation) is currently the gold standard and treated before 2–2.5 years of age**(6).**

CONCLUSION:

MPS I-H is a rare, life-threatening multisystem disorder.It is the most frequent type of MPS reported.Early detection of the disease and appropriate management through a multidisciplinary approach is recommended to improve the quality of life. Primary care providers and pediatricians must increase their awareness of MPS I-H, to better recognize the peculiar signs and symptoms and promptly refer the child for futher Biochemical screening and Molecular diagnostics.

REFERENCES:

1. Grech R, Galvin L, O'Hare A, Looby S. Hurler syndrome (Mucopolysaccharidosis type I). BMJ Case Rep. 2013 Mar 25; 2013: bcr 2012008148.doi: 10.1136/bcr-2012-008148. PMID: 23531928; PMCID: PMC3618758.
2. Sharma S, Sabharwal JR, Datta P, Sood S. Clinical manifestation of Hurler syndrome in a 7 year old child. Contemp Clin Dent 2012;3:86-9.
3. Thomas J. A. Lehman, Nicole Miller, Becky Norquist, Lisa Underhill, Joan Keutzer, Diagnosis of the mucopolysaccharidoses, *Rheumatology*, Volume 50, Issue suppl_5, December 2011, Pages v41–v48, https: // doi. org/ 10. 1093/ rheumatology/ ker390
4. Filocamo M, Tomanin R, Bertola F, Morrone A. Biochemical and molecular analysis in mucopolysaccharidoses: what a paediatrician must know. Ital J Pediatr. 2018 Nov 16;44(Suppl 2):129. doi: 10.1186/s13052-018-0553-2. PMID: 30442161; PMCID: PMC6238298.
5. Scott HS, Anson DS, Orsborn AM, Nelson PV, Clements PR, Morris CP, Hopwood JJ. Human alpha-L-iduronidase: cDNA isolation and expression. Proc Natl Acad Sci U S A. 1991;88:9695–9.
6. Parini R, Deodato F, Di Rocco M, Lanino E, Locatelli F, Messina C, Rovelli A, Scarpa M. Open issues in Mucopolysaccharidosis type I-Hurler. Orphanet J Rare Dis. 2017 Jun 15;12(1):112. doi: 10.1186/s13023-017-0662-9. PMID: 28619065; PMCID: PMC5472858.