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HEREDITARY OROTIC ACIDURIA WITH UNUSUAL PRESENTATION- A RARE CASE REPORT

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ABSTRACT Hereditary orotic aciduria (HOA) is an extremely rare inborn error of pyrimidine metabolism. It results from a defect in the uridine-5-monophosphate synthase (UMPS) gene. It can result in megaloblastic anemia, developmental delay and crystalluria. Molecular genetics is the confirm diagnostic modality. Uridine triacetate is the only established treatment. We thus report a case of 13 month male child having developmental delay with regression, dysmorphic facies, nystagmus, skeletal abnormalities and massive hepatosplenomegaly with past history of repeated LRTI. After clinical evaluation, an impression of storage disorder was presumed. Bicytopenia was also obtained in CBC with high MCV. After detailed evaluation with haematological, bone marrow, TMS and GCMS of urine, a diagnosis of hereditary orotic aciduria was established. Although extremely rare, hereditary orotic aciduria should be suspected in any child with megaloblastic bone marrow, immunodeficiency or when developmental delay and anemia coexist.

KEYWORDS : hereditary orotic aciduria, pyrimidine, UMPS, megaloblastic anemia, GCMS

INTRODUCTION

Hereditary orotic aciduria is a rare inborn error of pyrimidine metabolism inherited as an autosomal recessive disorder[1]. Its birth prevalence is <1/1,000,000 live birth[2,3]. It affects men and women equally[2]. It is caused due to Uridine Monophosphate Synthase (UMPS) deficiency located on long arm of chromosome 3 [4]. It is associated with deficient activity of last two steps of de novo pyrimidine synthetic pathway resulting in decreased levels of UMPS enzyme. This eventually result in excessive accumulation of orotate and orotic aciduria [5]. Clinically, pyrimidine disorders may often be overlooked because they are rare and their symptoms not highly specific. There have been only about twenty identified cases worldwide[6]. So we are reporting a case of UMPS deficiency having megaloblastic anemia along with additional unusual and atypical presentation to highlight upon considering this disorder as possible cause of anemia and developmental delay.

CASE STUDY

A 13month male child born of 3rd degree consanguineous marriage admitted at MKCG, Berhampur with chief complaints of delayed milestones with some regression since 7 months and distension of abdomen for 5 months. He had attained rolling over and sitting with support by 6 months which was lost later and other milestones like sitting and standing without support was still not attained. There was no association of any apparent visual or hearing impairment or no peculiar odour of urine. There was past history of repeated URTI and LRTI. His most serious episode was 3 months back when he was admitted for 4 days. Antenatal history was uneventful. He was a term baby /normal vaginal delivery/ delayed cry and received phototherapy for 2 days on day 3 of life for neonatal jaundice. There was no family history of unexplained fetal loss or sibling death.

On examination, he had craniosynostosis, frontal and parietal bossing, dysmorphic facies like protrusion of eyeball with wide open eyes ,depressed nasal bridge, hypertelorism, hypertrophy of gums (fig 1). He also had short neck, short stature, short limbs with bony abnormality around wrist and elbow joint and also slight backward curving in lumbosacral area. Some pallor is present with no genital abnormality. Per abdomen examination revealed massive hepatosplenomegaly(fig 2). CNS examination revealed nystagmus, hypotonia of all limbs, CVS examination showed no abnormality . With suspected inborn error of metabolism (IEM), various modalities of investigation were sent.

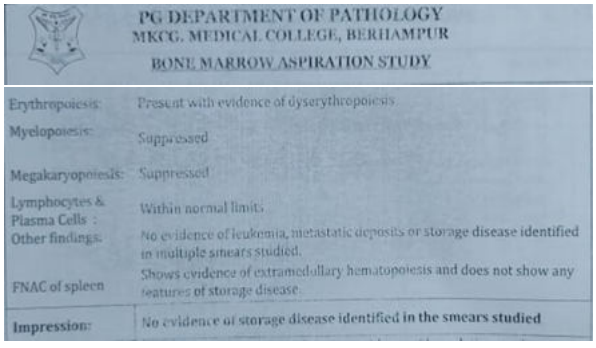
Investigation- CBC revealed Hb-6.2g/dl, TLC-16,870, platelet-32,000 (bicytopenia), peripheral smear suggestive of macrocytic anemia with MCV-105fl . ABG- no acidosis, urine ketone bodies and reducing sugar nil, sickling negative, eye examination-blue sclera, megalocornea, fundoscopy normal, USG B Scan- anechoic vitreous. Xray chest showed spatula shaped ribs. Thus, presuming it to be an entity of storage disorders either mucopolysaccharidosis or lipidoses, bone marrow was done which showed no features of storage diseases(fig 3), splenic aspiration was also normal. Urinary glycosaminoglycans(GAG) absent and Tandem mass spectrometry (TMS) of blood revealed elevated Octadecenoylcarnitine seen in carnitine Acyl-carnitine translocase/ carnitine palmitoyl-transferase type II deficiency. GCMS analysis of urine showed high orotic aciduria (fig 4). Finally diagnosis of hereditary orotic aciduria was made on the basis of history, examination followed by detailed investigation eliminating other causes of IEM. Molecular genetic testing of UMPS gene couldnot be done due to lack of facility.

Patient was started on tablet uridine triacetate 250 mg twice daily @ 65mg/kg/day and parents were counselled about the severity of the disease, possible outcome and necessity of follow up of clinical, immunologic, hematologic and biochemical response. They were also counselled regarding importance of genetic counselling and prenatal diagnosis during subsequent pregnancy so that termination of pregnancy can be done at the earliest.

Figure 1 dysmorphic facies

Figure 2 shows massive hepatosplenomegaly

Fig 3 BONE MARROW REPORT



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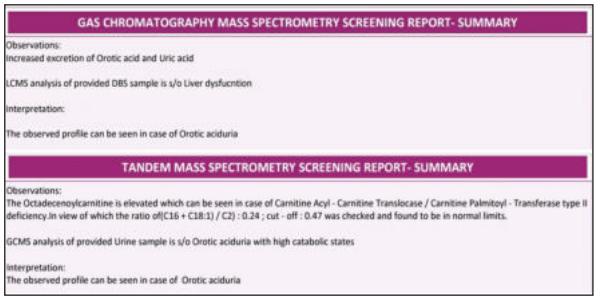
BONE MARROW ASPIRATION STUDY

Erythropoiesis:	Present with evidence of dyserythropoiesis
Myelopoiesis:	Suppressed
Megakaryopoiesis:	Suppressed
Lymphocytes & Plasma Cells :	Within normal limits
Other findings:	No evidence of leukemia, metastatic deposits or storage disease identified in multiple smears studied.
FNAC of spleen	Shows evidence of extramedullary hematopoiesis and does not show any features of storage disease.
Impression:	No evidence of storage disease identified in the smears studied

Fig 4 GCMS of urine, TMS of blood



GAS CHROMATOGRAPHY MASS SPECTROMETRY SCREENING REPORT- SUMMARY

Observations:
Increased excretion of Orotic acid and Uric acid

LCMS analysis of provided DBS sample is s/o Liver dysfucntion

Interpretation:

The observed profile can be seen in case of Orotic aciduria

TANDEM MASS SPECTROMETRY SCREENING REPORT- SUMMARY

Observations:
The Octadecenoylcarnitine is elevated which can be seen in case of Carnitine Acyl - Carnitine Translocase / Carnitine Palmitoyl - Transferase type II deficiency.In view of which the ratio of(C16 + C18:1) / C2) : 0.24 ; cut - off : 0.47 was checked and found to be in normal limits.

GCMS analysis of provided Urine sample is s/o Orotic aciduria with high catabolic states

Interpretation:
The observed profile can be seen in case of Orotic aciduria

DISCUSSION

Hereditary orotic aciduria is a rare autosomal recessive mutation of 3q13 [4]. UMPS is a bifunctional enzyme with catalytic sites for orotate phosphoribosyl pyrophosphate transferase(OPRT) and orotidine monophosphate decarboxylase (ODC). When one or both of these enzymes are impaired, conversion of orotic acid to uridine -5' PO_4 doesnot occur. This causes excessive accumulation orotic acid leading to orotic aciduria[7]. Two types of orotic aciduria have been reported- Type I has severe deficiency of both activities of UMP synthase and type II has ODC activity deficient while OPRT activity elevated[8].

These patients mostly present with symptoms before 12 months of life. Hallmarks of this disease are macrocytic hypochromic megaloblastic anemia refractory to vitamin B12 , iron and folic acid therapy and marked increase in orotic acid excretion in urine (crystalluria) [4,9]. CNS manifestations include intellectual disability, growth retardation, developmental delay, seizure, strabismus, motor impairment , hypotonia [9]. If untreated this disorder may lead to cardiac disease, stomatitis, failure to thrive, weakness, susceptibility to infection, crystalluria , subsequently ureteric obstruction and renal failure [4].Other signs include pallor, splenomegaly and hematuria.

In 1959, Hughley et al, first described HOA in a male child presented with megaloblastic anemia unresponsive to vitamin B12 and folic acid. In 2000, Besley et al described a case of UMPS deficiency without megaloblastic anemia and developmental delay[10].

Diagnosis is based on detailed patient and family history followed by laboratory studies CBC showing macrocytic hypochromic megaloblastic anemia, GCMS of urine revealing orotic aciduria, enzymatic defect demonstrated in liver, lymphoblasts, erythrocytes, leukocytes and skin fibroblasts[4]. Molecular genetic testing of UMPS gene is confirmatory.

Our patient also had macrocytic anemia, developmental delay, susceptibility to infection, but exception features were dysmorphic facies, skeletal abnormalities, massive hepatosplenomegaly and nystagmus which led to confusion in diagnosis. So after exclusion of storage disorder by bone marrow and urinary GAG, Tandem mass spectrometry and GCMS of urine assisted in establishing the diagnosis of hereditary orotic aciduria. Hence our case is a new unique case with atypical presentation of hereditary orotic aciduria.

In 2015, US food and drug administration (FDA) approved a treatment called uridine triacetate (Xuriden)[11]. It is administered at a dose of 50-300 mg/kg/day for lifetime. it bypasses the missed enzyme and provides body with a source of pyrimidine. Clinical trials investigating this medication have showed improvement in growth, anemia, decrease in orotic acid level in urine and restoration of normal developmental milestones [2]. Late detection does not cause reversal of neurological deficit and may lead to coma, seizure or death. The long term prognosis in uncomplicated cases is good.

CONCLUSION

Although extremely rare, HOA should be suspected in any child when megaloblastic anemia and developmental delay coexist. Early diagnosis and treatment of hereditary orotic aciduria are important prerequisites to prevent permanent disabilities and have better outcome by altering the disease course.

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