Tyrosinemia Type 1- A Rare Inborn Error of Metabolism

Authors
Dr Akshay Wanvat¹, Dr Shaista Parween², Dr Snehal Sonune³, Dr Ankita Kamble⁴

¹Resident Doctor, Department of Paediatrics, Grant Government Medical College and JJ Group of Hospitals, Mumbai
²Assistant Professor, Department of Paediatrics, Grant Government Medical College and JJ Group of Hospitals, Mumbai
³Resident Doctor, Department of Paediatrics, Grant Government Medical College and JJ Group of Hospitals, Mumbai
⁴Resident Doctor, Department of Paediatrics, Grant Government Medical College and JJ Group of Hospitals, Mumbai

Introduction
Tyrosinemia type 1 is an autosomal recessive inherited metabolic disorder attributed to deficiency of fumarylacetoacetate hydrolase (FAH), which is a terminal enzyme in the metabolism of tyrosine. The gene for this enzyme has been mapped to the long arm of chromosome 15. While primarily synthesized in the liver, FAH is also synthesized at moderate amounts in kidneys, adrenal glands, lungs, heart, intestines, stomach, pancreas, lymphocytes and skeletal muscles. The HT1 frequency worldwide is about 1 in 100,000 individuals.

Case Report
9 month old female child 2nd by birth order, born of non consanguineous marriage presented to our institute with history of vomiting and loose stools 2 months back and abdominal distension and lack of weight gain since last two months. There was no history of fever, bilious vomiting, insect bite, worms in stool, no bleeding manifestations, no peri-orbital or pedal edema. Birth history was suggestive of normal delivery and baby cried immediately after birth. Birth weight and length were as per gestational age.

Lab investigations done was suggestive of CBC hemoglobin 6.7 gm/dl, WBC 9090/mm³ and platelet 255000/mm³. Her coagulation profile was deranged (PT 25.6 and INR 1.97) but no bleeding manifestations present. Liver function test showed albumin 3.15, SGOT 74.5, SGPT 34.2, total Bilirubin 0.42, GGT 96 U/L, Alkaline phosphatase 831IU/L, serum ammonia 97.2ug/fl, Alpha-fetoprotein 43684ng/ml. Hepatitis marker were negative. Stool routine microscopy showed 15-25 pus cells/hpf and occult blood positive with
8-10 RBC/hpf but no reducing substance was present in stool. Renal function test and serum electrolyte were within normal limits. USG abdomen with portal vein Doppler done was suggestive of borderline hepatomegaly (8 cm) with altered liver echotexture suggestive of liver parenchymal disease and bilateral bulky kidney (Right kidney 8.6 x 4.7 cm and Left kidney 8.9 x 5.4 cm) with marginally raised cortical echogenicity and maintain corticomedullary demarcation (creatinine 0.69) and minimum ascitis. TMS and urine GCMS were sent which showed as screening test positive for succinylacetone present in urine and blood. Genome sequencing for FAH gene was sent, which came positive. Thus the diagnosis of tyrosinemia type 1 was made. Child was started on nitisinone and dietary modification to prevent tyrosine and phenylalanine in diet were done.

**Discussion**

Tyrosinemia has three distinctive types. Type I is characterized by progressive liver disease, increased risk of hepatocellular carcinoma, neurological crises and renal tubular dysfunction. It is also characterized by hypophosphatemic rickets. In acute type, hepatic insufficiency develops before six months of age as a result of...
micro and macronodular cirrhosis. In subacute type however, hepatomegaly, irregular bleeding and rickets are observed after six months. Chronic type manifests itself with hepatomegaly, rickets and growth retardation after one year of age\[3\]. Tyrosinemia type II, which is also known as oculocutaneous tyrosinemia, develops as a result of the deficiency of hepatic tyrosine amino transferase. Clinical findings include mental and motor retardation, corneal ulcerations and hyper keratotic lesions of the digits, palms and soles\[4\]. In tyrosinemia type III, there is lack of 4-hydroxyphenyl- pyruvate dioxygenase enzyme. All the patients suffer from growth retardation, convulsions, and ataxia. The most distinguishing characteristic of type I tyrosinemia is liver and kidney involvement\[4\], as seen in our patient

In a study conducted on 32 tyrosinemia type I patients, nephromegaly (47%), hyperechogenicity of kidneys (47%) and nephrocalcinosis (16%), aminoaciduria (82%), hypercalciuria (67%), tubular acidosis (59%), decreased glomerular filtration rate (48%) were found\[5\]. Our patient had most of these abnormalities including decreased tubular phosphorus reabsorption and aminoaciduria. Another study, conducted on 8 patients, reports nephromegaly, tubulopathy and vitamin D resistant rickets in 50%, 80% and 50% of the patients respectively\[6\]. This defect leads to accumulation of toxic products which cause liver and kidney dysfunction\[7\]. Before the treatment with 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3 cyclohexanedione (NTBC), which prevents the accumulation of toxic metabolites by inhibiting the tyrosine catabolism upstream from the primary enzymatic defect, patients have severe liver dysfunction, renal tubulopathy, cardiomyopathy, porphyria-like syndrome, and hepatocellular carcinoma and often need a liver transplantation\[8\]. Nevertheless, patients under NTBC and dietary treatment shown to have lower IQ, school problems, impaired motor control, and problems with executive functioning and social cognition\[9\].

References

9. van Ginkel, WG, Jahja, R, Huijbregts, SC. Neurocognitive outcome in tyrosinemia type 1 patients compared to healthy controls. Orphanet J Rare Dis. 2016;11(1):87. Google Scholar | Crossref | Medline