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Tyrosinemia Type 1- A Rare Inborn Error of Metabolism

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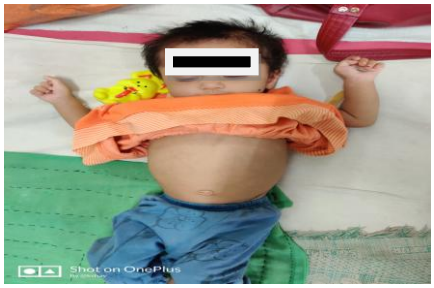
Introduction

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[1]. 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[1]. The HT1 frequency worldwide is about 1 in 100,000 individuals.[2]

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 periorbital 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.

On examination child was cachexia with distended abdomen and visible dilated abdominal veins. The anthropometric measurements should weight of 5.5 kg and height of 60 cm. weight for height was between -2 to -3 SD.



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.

PID NO: P81210000007
Age: 11 Month(s) Sex: Female

Metro healthcare
Shop no 4, mohamedi manzil 68 c,mohamed ali road,mumbai-400003. zone: c-04a(30)
PROCESSING LOCATION:- Metropolis Healthcare Ltd, Unit No. 409- 416, 4th Floor, Commercial Building-1, Kohinoor Mall, Mumbai-70

Registered On: 29/07/2021 01:58 PM
Collected On: 29/07/2021 1:58PM
Reported On: 30/07/2021 07:05 AM

Investigation	Observed Value	Unit	Biological Reference Interval
AFP-Alpha Feto Protein (Serum,ECLIA)	43684	ng/ml	<= 7 Please note change in Reference range and method

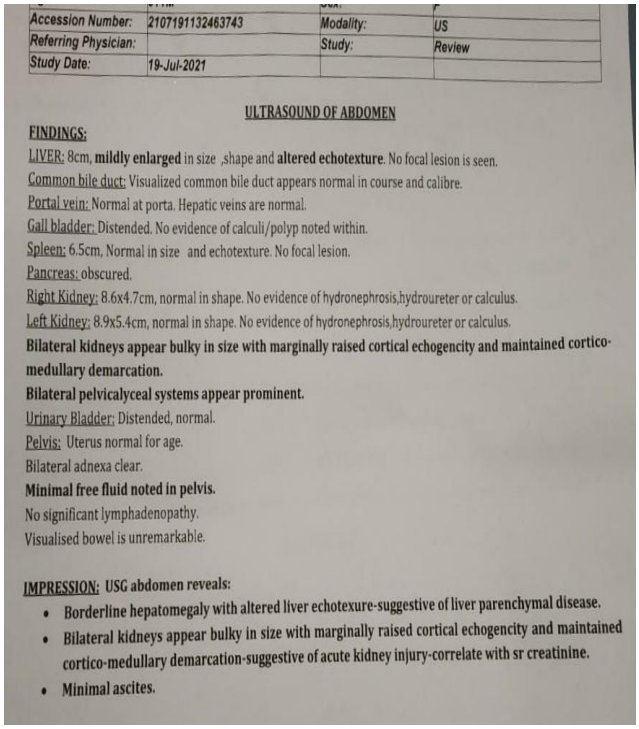
Medical Remarks: Rechecked
Interpretation:

Gestational Week	Regressed Medians (ng/mL)
14	27.9
15	30.9
16	36.1
17	40.4
18	48.3
19	54.8

1. The primary malignancies associated with AFP elevations are hepatocellular carcinoma and non-seminomatous germ cell tumors. Other gastrointestinal cancers like gastric, pancreatic occasionally cause elevations of AFP. Multiple benign disorders like cirrhosis, viral hepatitis, pregnancy are associated with AFP elevations. Level above which benign disease is considered unlikely is 500 ng/ml .
2. Range for newborns is not established, however neonates have elevated AFP levels (>100,000 ng/mL)(conversion 1 IU/ml x 1.21 = 1ng/ml) that rapidly fall to below 100 ng/mL by 150 days & gradually return to normal by one year. Ref - Tsuchida Y et al: Evaluation of alpha-fetoprotein in early infancy. J Ped Surg 1978 April;13(2):155-162 .

-- End of Report --

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 4.7cm and Left kidney 8.9x5.4 cm) with marginally raised cortical echogenicity and maintain corticomedullary demarcation (creatinine 0.69)and minimum ascitis.



Accession Number:	2107191132463743	Modality:	US
Referring Physician:		Study:	Review
Study Date:	19-Jul-2021		

ULTRASOUND OF ABDOMEN

FINDINGS:

LIVER: 8cm, **mildly enlarged** in size ,shape and **altered echotexture**. No focal lesion is seen.
Common bile duct: Visualized common bile duct appears normal in course and calibre.
Portal vein: Normal at porta. Hepatic veins are normal.
Gall bladder: Distended. No evidence of calculi/polyp noted within.
Spleen: 6.5cm, Normal in size and echotexture. No focal lesion.
Pancreas: obscured.
Right Kidney: 8.6x4.7cm, normal in shape. No evidence of hydronephrosis,hydroureter or calculus.
Left Kidney: 8.9x5.4cm, normal in shape. No evidence of hydronephrosis,hydroureter or calculus.
Bilateral kidneys appear bulky in size with marginally raised cortical echogencity and maintained cortico-medullary demarcation.
Bilateral pelvicalyceal systems appear prominent.
Urinary Bladder: Distended, normal.
Pelvis: Uterus normal for age.
Bilateral adnexa clear.
Minimal free fluid noted in pelvis.
No significant lymphadenopathy.
Visualised bowel is unremarkable.

IMPRESSION: USG abdomen reveals:

- **Borderline hepatomegaly with altered liver echotexure-suggestive of liver parenchymal disease.**
- **Bilateral kidneys appear bulky in size with marginally raised cortical echogencity and maintained cortico-medullary demarcation-suggestive of acute kidney injury-correlate with sr creatinine.**
- **Minimal ascites.**

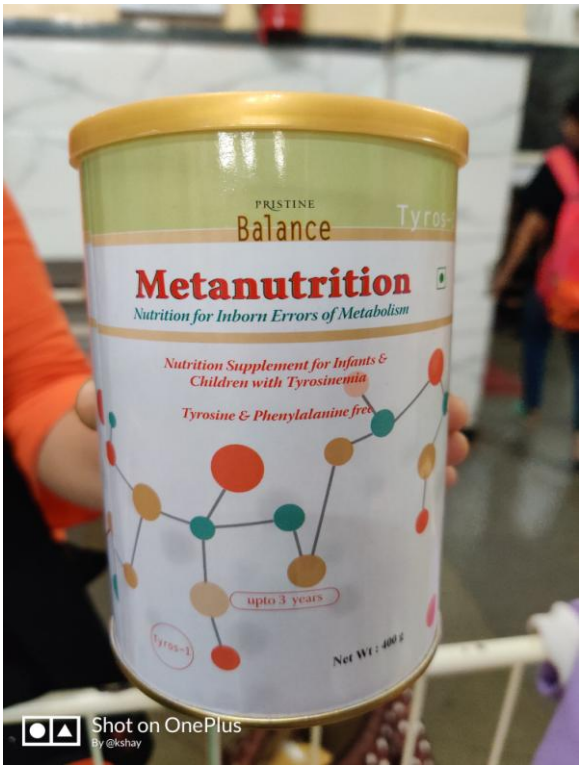
TMS and urine GCMS were sent which showed as screening test positive for succinylacetone present in urine and blood. Genome sequencing for FAH gene was sent, which came positive. Thus the diagnosis of tyrosinemia type 1 was made.

Package	Gender	DOB/Age	Referred By
NBS Duo	FEMALE	09/09/2020 (10 Mths 14 Days 6 Hrs)	Dr. Poonam Mane
Hospital name	**City**	**Pre Term / Full Term**	**Baby Weight (Kg)**
T T HOSPITAL	South Mumbai	Full term	3.450
Specimen Source	**Specimen Notes**	**Collection Date & Time**	**Received Date & Time**
Heel Prick and Urine	Pending	24/07/2021 15:30	25/07/2021 15:30
Date of Report & time	**Blood Transfusion**	**Transfusion Date**	**Special Feeds / IVF / TPN/ Supplements**
26/07/2021 15:45	NO	NO	Yes

INBORN ERRORS OF METABOLISM (IEM) SUMMARY REPORT

Sr. No.	Test Methodology	Result	Test Type	Page
1	TANDEM MASS SPECTROMETRY SCREENING REPORT	Positive	Screening	2
2	GAS CHROMATOGRAPHY MASS SPECTROMETRY SCREENING REPORT	Positive	Screening	4

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]. Tyrosinema 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-trifluoromethylbenyol)-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]

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