Tyrosinemia type 1: A case report

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Abstract

Tyrosinemia Type 1 is a rare inherited metabolic disorder attributable to a deficiency of enzyme fumarylacetoacetate hydrolase. It has an autosomal recessive pattern of inheritance. The accumulation of tyrosine and its toxic metabolites succinylacetone and succinyl acetoacetate in various tissues leads to the characteristic hepatic failure, renal dysfunction, and neurological crisis. Here, we present a case of a 7-month-old female infant who was brought with complaints of jaundice, dyspnea, altered level of consciousness, refusal to feed. We highlight the need for early diagnosis, including prenatal testing and initiating treatment at the earliest, which goes a long way not only in the survival, but also the quality of life in these patients.

Key words: *Inborn error of metabolism, Neonatal hyperbilirubinemia, NTBC therapy, Prenatal diagnosis, Tyrosinemia*

Tyrosinemia Type 1 is an autosomal recessive inborn error of amino acid, tyrosine metabolism. The enzyme deficient is fumarylacetoacetate hydrolase (FAH) coded by *FAH* gene that is located on chromosome 15q25.1 [1,2]. The altered *FAH* gene produces an unstable or inactive enzyme, which results in reduced or absent FAH activity, which in turn results in accumulation of fumaryl- and maleyl-acetoacetate causing cellular damage. Fumaryl- and maleyl-acetoacetate are reactive compounds and have not been identified in tyrosinemia patients. Succinylacetone, however, is derived from these metabolites by reduction and decarboxylation, is elevated in serum and urine from the patients.

Tyrosinemia is clinically heterogeneous. Symptoms may start during the first few months (acute type), in the second half of the 1st year (sub-acute type) or in the following years up to adulthood (chronic type). In the acute type, manifestations of hepatic failure predominate. Children older than 6 months of age present with signs of renal disease, rickets, and/or neurologic crisis, which include change in mental status. Abdominal pain, peripheral neuropathy, and seizures may compound the illness at any stage. Those children who are not treated with nitisinone and a low-tyrosine diet and who survive the acute onset of liver failure are at high risk of developing hepatocellular carcinoma [3]. The effective therapeutic use of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) in tyrosinemia prevents the accumulation of fumarylacetoacetate and its conversion to succinylacetone.

CASE REPORT

A 7-month-old female infant brought with fever, difficulty breathing, associated with chest in drawing, grunting and mouth breathing for 4 days. The baby was lethargic and drowsy and refusing to feed for 3 days. There was a history of decreased urine output since 2 days. She was the 5th offspring born to 2nd degree consanguineous couple, after an uneventful pregnancy. She had complaints of yellowish discoloration of skin and eyes since 1 month of age and also distension of abdomen since the last 4 months, which was slowly progressive and accompanied with frequent episodes of vomiting following feeds. She was admitted previously for 15 days at 6 months of the age for similar complaints. The mother had noticed the infant and its urine to be having a distinct odor similar to that of boiled cabbage. However, there was no history of convulsions, blood in stool or vomitus, nose bleeds or cyanosis. The child attained developmental milestones at the appropriate age except that it finds difficult to go prone due to the distended abdomen. The couple had lost a son to similar complaints at the age of 6 months. Child was fully immunized for date.

On physical examination, the patient appeared sick, icteric, febrile and drowsy. There was marked pallor and respiratory distress. The patient weighed 5.3 kg (66.25% of normal weight for age) and the anterior fontanelle was 3 cm × 3 cm wide. Examination of the abdomen revealed distended abdomen, everted umbilicus, liver was barely palpable below the right costal margin, spleen was palpable 3 cm below the left costal margin. Fluid thrill was present. Chest examination showed

in-drawing of chest, hurried breathing, wheeze audible close to the chest wall, apex beat in the 5th intercostal space on the left side at midclavicular line. The chest expansion was barely 1-1.5 cm. On auscultation, bronchial breath sounds heard, associated with widespread rhonchi. Heart sounds were normal without any added sounds. Examination of central nervous system revealed a drowsy infant responding only to painful stimuli, not interested in surroundings or play. Rest of the nervous system examination was unremarkable.

Her hemoglobin was 9.8 g/dl and leukocyte counts were raised (18,100/mm^3) with normal platelet counts. Peripheral smear examination showed normocytic normochromic anemia with leukocytosis. Blood urea and serum creatinine were markedly elevated (56.6 and 2.8 mg/dl respectively). Liver function test revealed conjugated hyperbilirubinemia (total bilirubin - 35.5, direct - 29.6 and indirect bilirubin - 5.9 mg/dl). Hepatic enzymes were also elevated (aspartate aminotransferase – 198 U/L, alanine aminotransferase – 99 U/L, alkaline phosphatse - 625.1 IU/L). Prothrombin time (PT) was 27 s (control 15 s) and partial thromboplastin time (PTT) was 67.3 s (control 30 s). Ultrasonography of the abdomen showed contracted gall bladder, and moderate spleenomegaly features suggestive of obstructive jaundice.

The patient was put on 3 consecutive days of intramuscular injection of vitamin K; however, the prolonged PT and PTT were unresponsive and incompatible with liver function tests. Despite the grossly deranged coagulation profile, the patient had no history of bleeding tendency. Therefore, metabolic causes for acute liver failure were considered. Serum alpha-fetoprotein (AFP) level was extremely high >363,000 ng/ml (normal <9 ng/ml). Her tandem mass spectrometry revealed elevated tyrosine levels (Table 1).

In the light of these findings, the infant was diagnosed to have tyrosinemia Type 1. The patient was referred to our tertiary care from a peripheral center. Lack of awareness on the part of the parents to seek timely medical advice, delay in referral to a higher center caused a time lag in enrolling the patient on NTBC therapy. The prospect of liver transplantation was also considered. With the delay in diagnosis and to institute specific treatment and the feasibility of pediatric liver transplant being so bleak in our country, the patient, unfortunately, succumbed to the illness.

DISCUSSION

Tyrosinemia is an inborn error of tyrosine metabolism. It is of three distinct types. Tyrosinemia Type 1 is due to the deficiency of the enzyme FAH. Worldwide, Type I tyrosinemia affects about one person in 100,000. This is more common in the Saguenay-Lac St. Jean region of Quebec, it affects one person in 1846 [4]. Tyrosinemia I is an autosomal recessive disorder; therefore, the sex distribution is equal [5]. Type 2, Reichner Hanhart syndrome, is caused by a deficiency of tyrosine aminotransferase enzyme which leads to the characteristic occulocutaneous syndrome. Type 3 Tyrosinemia is due to deficiency of 4-hydroxypyruvate dioxygenase enzyme characterized by mental and motor retardation, seizures and intermittent ataxia [6].

Tyrosinemia type 1 is an inborn error of tyrosine catabolism characterized by progressive liver disease, renal tubular dysfunction, neurological crises and a dramatic improvement in prognosis following treatment with nitisinone. These changes are brought about by the deposition of amino acids such as tyrosine, methionine and toxic byproducts of amino acid metabolism like succinylacetone and succinylacetatoactetate. The diagnosis of tyrosinemia can be established by determination of succinylacetone in urine or serum and by assay of FAH activity in lymphocytes and fibroblasts [7]. The elevated levels of serum tyrosine and methionine provided key for the diagnosis in our patient, further strengthened by the deranged liver function parameters, and abnormal coagulation profile. Though, the infant was given a provisional diagnosis of neonatal hepatitis, the alarmingly high levels of AFP were indicative of intrauterine liver damage. AFP is elevated in certain conditions like the omphalocele, viral hepatitis, neonatal iron storage disorders, hepatocellular carcinoma, extrahepatic biliary atresia [8].

Prenatal diagnosis of tyrosinemia is possible by analysis of succinylacetone in amniotic fluid supernatant and by assay of FAH in cultured amniotic fluid cells or a chorionic villus material [9]. Any infant who is jaundiced at 2-4 weeks old, even if he looks otherwise well should undergo methodical and comprehensive diagnostic investigations. Differential diagnoses include neonatal hemochromatosis, classic galactosemia, hereditary fructosemia, and citrullinemia type 2 which can be ruled out by investigations as listed in Table 2.

Table 1: Screening for inborn errors of metabolism by tandem mass spectrometry

Amino acid	Test	Normal range
Tyrosine	528.68 μmol/L	17-250 μmol/L
Methionine	51.82 μmol/L	1-44 μmol/L
Phenylalanine	32.16 μmol/L	21-136 μmol/
Citrulline	32.16 μmol/L	0-45 μmol/L

Table 2: Differential diagnoses for tyrosinemia Type I

Neonatal hemochromatosis	Elevated transferrin saturation and serum ferritin levels
Classic Galactosemia	Quantitative erythrocyte galactose-1-phosphate uridyltransferase analysis
Hereditary fructosemia	Enzyme analysis, genetic testing
Citrullinemia Type 2	Tandem mass spectrometry

Although, it greatly slows the progression of the disease, permanent liver damage is inevitable [10]. Osteoporosis and rickets resulting from renal tubular damage are treated by correction of acidosis, restoring calcium and phosphate balance, and administration of 25-hydroxy-vitamin D. Liver transplantation is the treatment of last resort when patients fail to respond To NTBC therapy or develop hepatocellular cancer. Early nitisinone treatment reduces the need for liver transplantation in children with tyrosinemia Type 1 and for those progressing to liver transplantation despite use of NTBC results in improved post-transplant renal function.

CONCLUSION

When there is a positive family history known as seen in our case report, prenatal testing can be used to clarify the genetic status of at-risk sibling before birth. As clinicians, we need to look beyond infections and consider the possibility of other rarer causes that often go undiagnosed.

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