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Case Report Open Access

Diagnosis and Treatment of Tyrosinemia: A Case Series

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Abstract

Background: Hepatorenal tyrosinemia is inborn error of metabolism that affects numerous organs, particularly liver, kidneys, and peripheral nerves. Tyrosinemia is rarely reported from India due to lack of diagnostic facilities. We are reporting 3 male infants, who presented with varied clinical manifestations. All 3 of them had elevated 4-hydroxyphenyllactic acid levels in urine and elevated alpha-fetoprotein but no evidence of hepatocellular carcinoma.

Outcome: One infant is on low tyrosine-phenylalanine diet and under regular follow-up, the other two however, lost follow-up.

Conclusion: It is important to diagnose tyrosinemia as both treatment and prenatal diagnosis are possible.

Keywords: Tyrosinemia; Succinylacetone; 4-hydroxyphenyllactic acid; Inborn error; Metabolism

Case Presentation

Case 1: 52 days boy born to second degree consanguineous parents. Patient was born through uneventful pregnancy and delivery. He presented with complaints of progressive yellowish discoloration of eyes, high colored urine, and abdominal distension since birth. Weight and length were less than 3rd centile. Physical examination revealed deep icterus, firm non-tender hepatomegaly with span of 9 cm, irregular surface and rounded border, firm non-tender splenomegaly 2.5 cm below left costal margin. Cardiac, respiratory, central nervous system examinations were normal.

Initial investigations revealed direct hyperbilirubinemia 12.8 (normal up to 0.25 mg/dl), alanine aminotransferase 183 (normal up to 40 µ/l), gamma glutamyl transferase 71 (normal up to 204 µ/l), international normalised ratio 2.41, prothrombin time 30 seconds (normal range 11-16 seconds), Thyroid function was normal, congenital cytomegalovirus, toxoplasma gondii screen were normal, serum ferritin 859.3 (normal 150-450 ng/ml), serum iron 169 (normal 27-109 microgram/dl), transferrin 166 (normal 140-319 mg/dl), alpha feto protein 171320 (normal up to 28ng/ml), urine for ferric chloride was strongly positive, sepsis work up was unremarkable, ultrasonography abdomen showed contracted gall bladder with mild ascites.

As baby was passing persistent yellow color stool with jaundice since birth, visualisation of gall bladder on ultrasonography of abdomen, biliary atresia was unlikely. Since baby had early significant splenomegaly with elevated ferritin and alpha fetoprotein, positive urinary ferric chloride, normal ophthalmology evaluation, we narrowed our differentials to tyrosinemia, neonatal iron storage disorder (NISD). In view of correction of coagulopathy with Vitamin-K, normal transferrin saturation levels, possibility of tyrosinemia was considered over neonatal iron storage disorder. Urine organic acid profile showed elevated values of hippuric acid 466.02 (normal cut-off 21.54), 4 Hydroxyphenyllactic acid 217.14 (normal cut-off 12.51), 4 hydroxy phenylpyruvic acid 101.81 (normal cut-off 1.90), Hippuric 1 1330.60 (normal cut-off 336.99), succinylacetone was not detected. We made diagnosis of tyrosinemia type 3. Disease status was explained to parents. They were told need of nitisinone. Patient lost to follow up.

Case 2: 9 months male well thriving baby born to 3rd degree consanguineous parents was diagnosed to have severe anemia (microcytic hypochromic), melena and respiratory distress; he was referred after giving one unit of blood. On arrival baby was in impending respiratory failure with bilateral crepitations, wheeze. Per abdomen examination showed firm hepato-splenomegaly, examination showed dysmorphic features as flat facies, bilateral clinodactaly, and increased gap between first and second toes. Baby was managed with oxygen by non-rebreathing mask, propped up position, diuretics and nebulised bronchodilators.

Blood work up showed haemoglobin of 7.6 g/dl, total cell count 19900 (normal 6000-17500 cell/cu mm), platelet count 112000 platelet/µl, prothrombin time 54 seconds (normal up to 11-16 seconds), partial thromboplastin time 39 seconds (normal up to 30 seconds), international normalised ratio of more than 5.1, lactate dehydrogenase 688 µ/l (normal up to 572 µ/l), baby was managed with fresh frozen plasma, Vitamin-K, intravenous antibiotics. Repeat prothrombin time was 35 seconds, international normalised ratio 3.29 showed falling trends, 2D-ECHO was normal, ultrasound abdomen showed multiple well defined hyperechoic lesions in liver, peripheral smear study showed dimorphic population, complete haemogram of father was normal, mild hypochromic microcytosis with normal haemoglobin in mother.

Bone marrow examination showed normocellular marrow with dyserythropoiesis, absent iron stores, decreased megakaryocytes. One unit of packed cell transfusion was given, haemoglobin level raised to 8.9, respiratory distress settled, he was hemodynamically stable so discharged. After 2 weeks, baby was presented with features of congestive cardiac failure, respiratory distress, edema and progressive abdominal distension. Baby was initially managed with anti-congestive

cardiac failure measures, his work up showed total cells 24800 (normal 6000-17500 cell/cu mm), prothrombin time 43 seconds (normal up to 11-16 seconds), partial thromboplastin time 50 seconds (normal up to 30 seconds), chest x-ray showed right upper lobe pneumonia. Ultrasound abdomen showed mixed echogenic lesions occupying almost entire parenchyma of liver. Liver biopsy was suggestive of idiopathic neonatal hepatitis, urine for reducing substance, urine ferric chloride tests were negative, alanine transaminase 33 µ/l (up to 40 µ/l), alpha fetoprotein 26450 ng/ml (normal up to 28 ng/ml), urine for succinylacetone was 24.47 (ref. range 0%), 4-hydroxyphenyllactic acid 397.29 (ref. range 1.8%), n-acetyltyrosine 80.50 (ref. range 0%), so we made diagnosis of tyrosinemia type I. We explained need of NTBC to parents, hepatologist counselled parents for liver transplant. Family lost to follow up.

Case 3: 55 days male baby born to nonconsanguineous parents presented with history of acute onset seizures, irritability, and lethargy with increasing paleness, icterus besides depressed sensorium. Baby had features suggestive of raised intracranial pressure with acute encephalopathy, seizures, and anemia.

Measures were taken to control intracranial pressure with intravenous mannitol, head end elevation, airway was secured by invasive ventilation, intravenous anti-epileptics were added, haemoglobin was 6.2, total cell count 17600 (normal 6000-17500 cell/cu mm), platelet count 321000 platelet/µl, alanine aminotransferase 105 (normal up to 40 µ/l), aspartate aminotransferase 168 (normal up to 40 µ/l), bilirubin total 9.98 mg/dl, direct fraction of bilirubin 6.32 mg/dl, indirect fraction of bilirubin 3.66 mg/dl, lactate dehydrogenase 680 µ/l, prothrombin time 17 seconds (normal up to 11-16 seconds), partial thromboplastin time 37 seconds (normal up to 30 seconds), international normalised ratio 1.26. Reducing substance in urine was negative, brain computed tomography scan showed diffuse symmetrical hypodensities involving gray-white matter in bilateral cerebral hemisphere-possibly extensive infarcts, blood culture was sterile, alpha fetoprotein 5221 (normal up to 28 ng/ml), urine for succinylacetone was 1.53 (reference range 0%), 4-hydroxyphenyllactic acid 50.79 (reference range 1.8%), n-acetyltyrosine 25.54 (reference range 0%), so diagnosis of tyrosinemia type I was considered. Repeat computed tomography brain showed same features so poor prognosis was explained to parents and they decided to take discharge at request from hospital.

Parameter	Case 1	Case 2	Case 3
Age	52 days/male	9 months/ male	55 days/male
Bilirubin: T/D/I	17.98/12.8/5.18	1.23	9.98/6.32/3.66
PT (seconds)	30	54	17
PTT (seconds)	Not done	39	37
INR	2.45	>5.1	1.26
AFP ng/ml	171320	26450	5221
Urine for succinylacetone	Negative	24.47	1.53
Urine 4-hydroxyphenyllactic acid	217.14	397.29	50.79

Table 1: Comparison of test parameters among the cases.

Enzyme assays were not performed in any of these cases since nitisinone in India is unavailable, it's an orphan drug. We have to refer early for a liver transplant as it is curative. These treatment options were explained to all three patients and one patient is on low phenylalanine-tyrosine diet and other two lost to follow-up. Diagnosis of tyrosinemia was suggested by combination of early onset hepatic dysfunction and positive ferric chloride screen with raised alpha fetoprotein levels. The urine metabolites suggestive of tyrosinemia also add to high probability of type I tyrosinemia. The confirmatory tests were not available to confirm diagnosis further (Table 1).

Discussion

Hereditary tyrosinemia type I is an autosomal recessive disorder caused by deficiency of fumarylacetoacetate hydrolase (FAH), the last enzyme of tyrosine degradation. The disorder is characterized by severe liver disease associated with bleeding disorder, hypoglycemia, hypoalbuminemia, elevated transaminases, and secondary renal tubular dysfunction leading to hypophosphatemic rickets. Hepatocellular carcinoma may eventually occur. Onset varies from infancy to adolescence. In the most acute form patients present with severe liver failure within weeks after birth, whereas rickets may be the major symptom in chronic tyrosinemia. Untreated, patients die from cirrhosis or hepatocellular carcinoma at a young age [1]. Tyrosinemia type II is also known as Richner-Hanhart syndrome. It is caused by mutation in the TAT gene on chromosome 16q22. Tyrosinemia type III is caused by mutation in the HPD gene. The severe liver damage in tyrosinemia is the result of defective degradation of tyrosine [2]. Tyrosinemia is identified in neonatal screening programs using tandem mass spectrometry methods to detect elevated tyrosine and/or succinylacetone. Elevated tyrosine levels also occur as a nonspecific consequence of severe liver disease or transient tyrosinemia of the newborn, which responds to ascorbic acid treatment. Quantitative measurement of plasma tyrosine and blood or urine succinylacetone is performed after a positive neonatal screen. The diagnosis of tyrosinemia I is confirmed by an increased concentration of succinylacetone, DNA testing is available for some mutations.

Prenatal diagnosis of tyrosinemia is possible either by the detection of succinylacetone in the amniotic fluid [3] or by measurement of fumarylacetoacetase in cultured amniotic cells. Holme and Lindstedt stated that since the first trial of NTBC treatment for type I tyrosinemia in 1991, over 220 patients had been treated by the drug using a protocol that included regular follow-up with reports of clinical and laboratory investigations. Only 10% of the patients had not responded clinically to NTBC treatment. In half of these patients, successful liver transplantation had been performed, which further reduced the mortality rate during infancy to 5%. The data indicated a decreased risk for early development of hepatocellular carcinoma in patients who started treatment at an early age. Of the 101 patients aged 2 to 8 years who had started NTBC treatment before 2 years of age, no patient developed cancer after 2 years of age [4].

Outcome and prognosis of tyrosinemia type I significantly improved after introduction of 2-(2-nitro4-trifluoromethyl benzoyl) cyclohexane-1, 3-dione (NTBC) [5,6]. NTBC acts as a strong inhibitor of hydroxyphenylpyruvate dioxygenase (HPPD) that prevent tyrosine degradation and stop the production of toxic metabolites such as maleylacetoacetate, fumarylacetoacetate, succinyl acetoacetate, succinyl acetone and 5-aminolevulinic acid, which are accounting for the renal, hepatic and neurological manifestation of tyrosinemia type I. Succinyl acetone and 5-aminolevulinic acid are responsible for

neurological symptom in this disease [7,8]. NTBC stops hepatic and neurologic complications and has protective effect against the hepatocellular carcinoma in tyrosinemia if started early in life [7,9]. NTBC cannot entirely prevent liver cancer, so regular follow-up should be done in these patients [6]. NTBC blocks para-hydroxy phenyl pyruvic acid dioxygenase (P-HPPD), the second stage in the path of destruction of tyrosine, inhibits the accumulation of fumaryl acetoacetate and its modification to succinylacetone. These processes stop the production of 5-aminolevulinic acid, fumaryl acetoacetate, succinyl acetoacetate, succinylacetone and maleylacetoacetate that cause hepatic, renal and neurological symptoms [6-9].

Therefore, discontinuation of NTBC rapidly increases fumaryl acetoacetate, succinyl acetoacetate, succinylacetone that had a major role in developing of neurological crises and subsequently respiratory failure [6,7]. NTBC rises the blood concentration of tyrosine, so dietary restriction of phenylalanine and tyrosine should be done immediately, to inhibit deposition of tyrosine crystals in the cornea [9]. A low-phenylalanine, low-tyrosine diet may also play a role in management of type I tyrosinemia. Tyrosinemia II and III are more benign forms of hereditary tyrosinemia. Blocked metabolism of tyrosine at earlier steps in the pathway is responsible, and succinylacetone is not produced. The clinical features include hyperkeratosis of palms and soles and keratitis, which can cause severe visual disturbance. Poor dietary compliance with type II tyrosinemia is associated with mild cognitive impairment. Treatment with a phenylalanine- and tyrosine-restricted diet is effective.

Conflict of Interest

None declared.

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