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Case Report

TYROSINEMIA TYPE I: A CASE REPORT AND REVIEW OF LITERATURE

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ABSTRACT
Tyrosinemia type called hepatorenal tyrosinosis, is a severe inborn metabolic disease affecting the tyrosine degradation pathway. It often presents with liver disease or liver failure with predominant bleeding tendencies, fanconi syndrome and/or rickets. Diagnosis is based on clinical features, increased tyrosine and methionine in plasma and the presence of succinyl acetone in urine. Prior to the availability of nitisinone the only definitive therapy for the treatment of tyrosinemia type I was liver transplantation. Untreated patient develops liver failure, cirrhosis with heapatocellular carcinoma, and end stage renal failure. Here we describe a two-month old infant presented with massive ascites with coagulopathy, hypoalbuminemia and mildly deranged liver enzymes. The diagnosis of Tyrosinemia type I was made on the basis of disproportionate liver synthetic dysfunction, high alpha feto protein levels and elevated urinary succinyl acetone levels.

Keywords: *Tyrosinemia Type I, Hepatorenal Tyrosinemia, Inborn Metabolic Disease*

INTRODUCTION
Tyrosinemia type I (hepatorenal tyrosinemia, OMIM No. 276700) is a rare autosomal recessive disorder, with clinical and pathological manifestations involving mainly the liver, kidney and peripheral nerves. The clinical findings range from severe hepatocellular dysfunction in early infancy to chronic liver disease. Tyrosinemia type I affects approximately one in 100,000 to 120,000 births (Mitchell *et al.* 2011). The disorder is common in Quebec (1 in 16,786 live births) and Scandinavia (De Braekeleer *et al.,* 1990). There have been few reports from India (Verma, 2000; Karnik *et al.,* 2004). We are presenting one case confirmed with urinary succinyl acetone levels.

CASES
A two-month-old boy was presented with generalised abdominal distension for 10 days and excessive irritability for 3 days. He was the only child born to a non-consanguineously married couple. The antenatal, perinatal and neonatal periods were uneventful. His birth weight was 2.6 kg. There was no history of fever, recurrent vomiting, jaundice, decreased urine output, bleeding from any site and seizures. The child was immunized for age. He was on breast feeds plus top feeds (diluted buffalo milk).
General physical examination was unremarkable except pallor and generalised abdominal distension with dilated, non-tortuous veins over abdomen. His weight was 6kg. On palpation child had firm hepatomegaly, 2cms below the right costal margin in midclavicular line and spleen was 1cm palpable below the left costal margin. There was free fluid in the abdomen. Examination of cardiovascular, respiratory and central nervous system revealed no abnormality.
The investigations performed were as follows: Haemoglobin 8.7 gm/dl, total leukocyte count 19010/cumm, differential count neutrophils 34%, lymphocytes 60%, monocytes 04%, and eosinophils 02%, peripheral smear – predominantly microcytic hypochromic cells. Renal functions (BUN and creatinine) and serum electrolytes were normal. Liver function tests showed mild derangement in liver enzyme (SGOT-71 IU/ml and SGPT-32 IU/ml) with disproportionate liver synthetic dysfunction (albumin-1.8 and INR-4.7). Total Billirubin was 3.6 mg/dl with direct component of 1.6mg/dl. The serum alpha-feto protein (AFP) levels were markedly raised (>2000IU/ml). Urine reducing substances were positive hence GALT (Galactose-1-phosphate uridyltransferase) assay was done which was normal.

Torch profile was negative. Urine protein and creatinine ratio was normal. There was raised methionine level on blood tandem mass spectroscopy.

An ultrasound study of the abdomen revealed mild hepatomegaly with normal echotexture with extensive periportal cuffing & peri gall bladder edema with gross ascites with mild splenomegaly, both kidneys were normal in size and echotexture. Liver biopsy could not be done because of coagulopathy. Ultrasound cranium was normal.

Urine succinyl acetone was elevated with elevation factor of 28 (normal-0). Enzyme fumarylacetoacetate hydroxylase (FAH) was not measured because of financial constraints. These results confirmed the diagnosis of hereditary tyrosinemia type 1 (HT1). Therapy with 2-(nitro-4-trifluoromethylbenzoyl) 1, 3-cyclohexanedione (NTBC) was advised and option of orthotopic liver transplantation was given. The family was provided genetic counselling and explained the inheritance with 25% risk of recurrence in a future pregnancy, and informed that prenatal diagnosis would be possible.

DISCUSSION

Hepatorenal tyrosinemia type 1 is a clinically severe inborn error that principally affects liver, kidney, and peripheral nerve (Mitchell *et al.,* 2011). The first case of typical clinical and biochemical picture of hepatorenal tyrosinemia was described by Sakai *et al.,* (1957). Since then, there have been over 100 case reports appearing in literature. Reports from the Indian subcontinent are few and without enzyme assay (Verma, 2000; Karnik *et al.,* 2004). HT1 is commonly suspected in Indiabut is under-diagnosed due to lack of availability of confirmatory tests (Verma, 2000).

The disease typically manifests in early infancy with acute hepatic crisis with hepatomegaly and bleeding diathesis precipitated by intercurrent illnesses inducing a catabolic state (McCormack *et al.,* 1992). The acute crisis may resolve spontaneously but usually persists as hepatomegaly, coagulation abnormalities and failure to thrive.

Cirrhosis of liver, hepatocellular carcinoma and death eventually occur early in life. Other features of tyrosinemia are peripheral neuropathy resembling acute porphyria and renal manifestations (Heath *et al.,* 2002).

Untreated children presenting before age of six months typically have acute liver failure with initial loss of synthetic function for clotting factors (Croffie *et al.,* 1999). PT and PTT are markedly prolonged and not corrected by vitamin K supplementation. Factor II, VII, IX, XI, and XII levels are decreased and factor V and factor VIII levels are preserved.

Paradoxically, serum transaminase levels may be only modestly elevated; serum bilirubin concentration may be normal or only slightly elevated, in contrast to most forms of severe liver disease in which marked elevation of transaminases and serum bilirubin concentration occur concomitantly with prolongation of PT and PTT. Resistance of affected liver cells to cell death may explain the observed discrepancy in liver function (Vogel *et al.*, 2004).

This early phase can progress to liver failure with ascites, jaundice and gastrointestinal bleeding. Children may have a characteristic odour of "boiled cabbage" or "rotten mushrooms". Infants occasionally have persistent hypoglycemia; some have hyperinsulinism. Untreated affected infants may die from liver failure within weeks or months of first symptoms (Baumann *et al.*, 2005).

The diagnosis of tyrosinemia type I should be further evaluated by quantification of urinary succinylacetone. The diagnosis in this patient is based on persistent ascites with mild hepatomegaly, disproportionate liver synthetic dysfunction, very high AFP levels, high methionine levels in plasma with urinary aminoaciduria and raised urine succinylacetone levels.

Molecular diagnosis is possible and is the preferred technique for prenatal diagnosis.In the presented case FAH was not measured because of financial constraints. FAH gene is located on chromosome 15 q and has 14 exons. Since the first report of the missense mutation n161 in the FAH mRNA, many mutations have been identified causing the disease (McCormack *et al*., 1992; Mitchell *et al.,* 2011; Rezvani, 2004). Of these, there are 4 common mutations observed in subjects from the Indian Subcontinent (McCormack *et al*., 1992).

Liver transplant is curative for the disorder and prior to NTBC was the mainstay of therapy. NTBC has revolutionized the therapy as it is effective within hours and abolishes or markedly diminishes the risk of hepatic or neurologic decompensation (Mitchell *et al.*, 2011).

The natural history of tyrosinemia type I in children who are treated with nitisinone is different from that in untreated children. Affected children younger than age two years who are treated with a combination of nitisinone and low-tyrosine diet are markedly improved compared to those children treated with low-tyrosine diet alone. The combined nitisinone and low-tyrosine diet treatment has resulted in a greater than 90% survival rate, normal growth, improved liver function, prevention of cirrhosis, correction of renal tubular acidosis, and improvement in secondary rickets (McKiernan, 2006; Masurel-Paulet *et al.*, 2008).

Although Holme *et al.*, (2000) and van Spronsen *et al*., (2005) reported hepatocellular carcinoma in individuals after years of nitisinone therapy, it is estimated that fewer than 5% of children placed on nitisinone therapy before age two years develop hepatocellular carcinoma by age ten years. Major issues regarding NTBC is confirmation of diagnosis, difficulties in import, and the cost involved. Recent clinical experience indicates that liver transplantation should now be reserved for those children who have severe liver failure at clinical presentation and fail to respond to nitisinone therapy or have documented evidence of malignant changes in hepatic tissue (Mohan *et al.*, 1999, Bartlett *et al*., 2014).

Prenatal diagnosis (PND) can be performed by measuring succinylacetone in amniotic fluid, FAH assay in chorionic villi taken at 10-12 weeks of gestation and using molecular technology to detect mutations in the FAH gene (Bijarnia *et al*., 2006).

Conclusion

It is important to diagnose this disorder early as early treatment significantly alters the prognosis and prenatal diagnosis of future pregnancies is possible.

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