Hereditary Tyrosinemia Type I, Presentation in a Two Month Old

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Abstract

Tyrosinemia is a metabolic disorder which manifests as increased levels of tyrosine in the blood. Hereditary Tyrosinemia Type I is one of the many causes of Tyrosinemia. It is due to the deficiency of the enzyme fumaryl acetoacetate hydrolase which leads to the rise in the serum levels of fumaryl acetoacetate and presents with a variety of different signs and symptoms such as neurological disorders, Hepatic and renal insufficiency and corneal depositions. It can be managed by the timely use of medication and dietary plan and fatality can be avoided if the disease is picked up in its earlier stages. We report a case of a 2-month-old baby with signs, symptoms and lab diagnosis suggestive of hereditary tyrosinemia. The case is discussed along with the drawbacks in our setup such as genetic testing and special tests required for a timely diagnosis for most metabolic disorders including neonatal liver disease such as hereditary tyrosinemia.

Keywords: Tyrosinemia, nitisinone, aminolevulinic acid, hepatocellular carcinoma, phenylalanine.
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Introduction

Tyrosinemia is a genetic disorder involving the metabolism of the amino acid tyrosine. It is characterized by abnormally high levels of tyrosine in blood and urine[1]. It presents typically in either infants or babies with jaundice and splenomegaly. There are many different kinds of tyrosinemia.

Cases of type 1 an autosomal recessive disorder. It is due to defect of fumaryl acetoacetase (FAA), which is the terminal enzyme of tyrosine degradation. The intermediate metabolites include maleyl- and fumaryl-acetoacetate. Both the latter two compounds are toxic at a local level and may cause mutagenic effects in the liver. The secondary metabolites is succinylacetone which has local and systemic effects and via its inhibition of porphobilinogen synthase can cause porphyria like neurological crisis[1,2].

Genetically FAA is on the short arm of chromosome 15 and more than 40 mutations have been described. Type 1 if left untreated may present with recurrent neurological symptoms which may last anywhere from one day to a week. These symptoms may include an altered mental status, peripheral neuropathy, abdominal pain and respiratory distress. Death in the untreated children occurs before 10 years of age[2] usually due to liver failure, neurological symptoms or hepatocellular carcinoma.

Tyrosinemia type II is due to the deficiency of enzyme "Tyrosine Transaminase". Deposition of the tyrosine crystals in skin and eyes is the characteristic feature of this subtype of metabolic disorder. On examination of the palms and soles, thickened areas of keratosis can be appreciated as well as development of painful ulcers in the cornea. Patients with type II Tyrosinemia often suffer from mental retardation.

Tyrosinemia type III is caused by the deficiency of 4-hydroxyphenylpyruvate dioxygenase (4-HPPD), an enzyme involved in the catabolic

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pathway of tyrosine[3]. It is a rare genetic disorder. The characteristic features of this subtype include seizures, mental retardation and intermittent type of ataxia.

Hereditary Tyrosinemia is a very rare disorder which can be overlooked. The delay in diagnosis can lead to mortality whereas, prompt treatment and diagnosis can prove to be very beneficial for the patient.

Case Report

A 2 month old boy (4.5 kg) was referred to Abassi Shaheed Hospital from another hospital with the chief complaints of Jaundice for one month, fever for a day and fits for a few hours. According to the mother, the baby was in his usual state of health when she noticed the baby had progressive jaundice. For the high-grade fever the child was given antipyretics which had no effect. He was rushed to the hospital during which he experienced an episode of jerky movements of the right upper and lower limbs.

The baby had no significant previous medical condition. According to the family history, the marriage between his parents is consanguineous. The mother had two abortions during her previous pregnancies in the first trimester. One baby boy expired at the age of 25 days due to pneumonia and a 2 and half month old baby girl expired due to sepsis previously. In addition, the mother has had one live baby boy who is 15 months old.

On inspection the boy looked very sick and inactive. He was afebrile. His vitals were taken which revealed his respiratory rate to be about 50 breaths per minute on average, pulse to be 140 beats per minute. His Glasgow Coma Scale score was 8/15. He was severely anaemic, mildly jaundiced and cyanotic. Abdominal examination revealed the liver to be 6 cms below the right costal margin. Spleen was also moderately enlarged and measured around 8 cms. On cardiovascular examination there was a wide splitting between the two heart sounds and his anterior fontanelle was open and bulging. Ophthalmic examination was normal.

Complete blood picture showed haemoglobin levels to be 8.3 g/dL, peripheral film showed microcytic, hypochromic anaemia. Total leukocyte count was elevated to 17.9X109. Platelets were about 29.5x10*3/microLitres. Liver Function Tests revealed total bilirubin to be 17.06mg/dl, Direct Bilirubin was increased to be 5.74 mg/dL, ALT was 104 iU/L, elevated alkaline phosphatase 700iU/L. Prothrombin Time was increased to 22 seconds. INR was raised to 2.04. A.P.T.T. was raised to 38 seconds where the control was 34 seconds. The direct coomb's test was negative. The 24 Hours urine for protein test showed 108.39 mg of protein. The G-6 PD levels were normal, Ceruloplasmin was in the normal range (28.28mg/dl) and serum A-1 antitrypsin levels were 1.52 gm/L (also in the normal range) whereas the Alpha Feto Protein was 1301.58 ng/ml (Normal range: 0-15 ng/ml) which suggested the diagnosis to be most likely Hereditary Tyrosinemia. Ultrasound abdomen showed only heptospleenomegaly, with no altered echo texture of the liver and no ascites. In this child emergency management included stabilization with fluids, correction of deranged coagulation parameters and anaemia. The parents were counseled about the disease and dietary advise given. Urine for succinylacetone and urinary delta-aminolaevulinic acid was to be sent, however, the parents did not return for follow-up, despite repeated counseling.

Discussion

Hereditary Tyrosinemia type 1 is fatal if left untreated. It results from the deficiency of fumaryl acetoacetate hydrolase; the last enzyme in the tyrosine metabolism. The frequency of HT1 worldwide is 1 per 100,000 individuals[4]. Since it is a relatively rare presentation, many cases go undiagnosed.

Succinyl acetone was the key finding urinary finding in the patients of Hereditary Tyrosinemia type I and was determined to be the product of succinyl acetoacetate decarboxylated. Succinyl acetoacetate is a structure that is a catabolic intermediate of tyrosine which led to the inference that the

enzyme deficient must be fumarylacetoacetase. This succinylacetone has been determined to be a mitochondrial toxin which inhibits phosphorylation during the Krebs cycle and causes dysfunctional transport through the membranes in kidneys. It also induces apoptosis of hepatic and renal tubular cells which explains the development of hepatocellular carcinoma in children with hereditary tyrosinemia. Elevated levels of urinary secretion of δ-aminolevulinic acid is linked to the inhibiton of heme synthesis. The intracellular accumulation of succinylacetone then manifests as neurological symptoms in such cases. Recent studies have suggested that it is this intracellular accumulation of fumarylacetoacetate itself that causes mitotic dysfunction and instabilities in the genome[5].

Many of these patients present with the appearance of failure to thrive initially. Complete blood count indicates anaemia and leukocytosis. The children generally present with failure to thrive, with a history of decreased nutritional intake. There can often be vomiting and diarrhoea which can progress to bloody stool, lethargy and jaundice. Patients presenting after one year of age, start walking late and may develop rickets[6]. Altered serum bilirubin concentration and altered liver enzymes is generally present. Alpha-fetoprotein levels were increased. Urine analysis showed proteinuria. Nearly all the above findings were seen in our patient.

Serum cholesterol levels are typically low due to liver damage. There are also instances of phosphaturia and an increased δ-aminolevulinic acid concentration in the urine. Urinary succinylacetone is the biochemical marker substance, and its presence is diagnostic for tyrosinemia I.

Imaging studies do not aid in the diagnosis of the condition but only to assess the extent of it in the patient. Baseline abdominal CT and MRI with contrast is used to look for adenomas or nodules in the liver and measure the renal size. To rule out the presentation of rickets, an X-Ray of wrist is used[2].

Increased levels of amino acid tyrosine and methionine often indicate that the point in the progression of the disease has been reached which depicts hepatic decompensation. The slow rising and decrease in the levels of alpha-fetoprotein levels in the blood can be associated with the development of hepatocarcinoma in the patient[7]. Hepatic histology is non-specific with steatosis and siderosis. The diagnosis is confirmed with measurement of FFA activity in fibroblasts or lymphocytes or by mutation analysis in families[5,7].

With the advent of advanced screening methods, patients are now diagnosed before the clinical decompensation occurs. Initial management is with phenylalanine- and tyrosine-restricted diet. NTBC (2-(2-nitro-trifluoromethylybenzoyl)-1,3-cyclohexenedione) which prevents the toxic metabolites to accumulate within a few days. This drug requires close monitoring with tyrosine levels kept less than 600 mol/l. NTBC is the best medical therapy after the diagnosis[8]. Medical management is focused towards the management of hepatic decompensation. Replenishment of the depleted coagulation factors is essential. After stabilization, NTBC should be started. Nutritional treatment is also imperative to ensure minimal phenylalanine-tyrosine intake.

Surgery has no role in stabilizing a critically ill child but Liver transplant can be done in patients who develop liver cirrhosis or hepatocellular carcinoma (HCC). Alpha fetoprotein should be done at least every three months and abdominal ultrasound every six months to monitor for HCC[9].

In our setup the baby's family could not be convinced for genetic testing despite counseling and levels of plasma tyrosine, phenylalanine and methionine (which would be increased three times the upper limit of normal), two of which were sent, but baby's parents did not bring him for follow-up. Also majority of the genetic tests are not easily available, in Karachi and are extremely expensive making it difficult to make a convincing diagnosis. Similarly urinary succinyl acetone a pathognomic but not an invariable finding, and urinary delta aminolaevulonic acid, could not be chased due to lost of follow-up. It is suggested that soon these

tests will be available at a low cost in our setting to allow an early diagnosis in such babies with appropriate counseling of family.

Conclusion

Even though it is rare, it is imperative for a doctor to pay keen attention to presenting features of these metabolic disorders such as hereditary tyrosinemia so that an early intervention can help prevent morbidity and liver transplantation in patients with cirrhosis.

Conflict of Interest

Authors have no conflict of interests and no grant/ funding from any organization for this case report.

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