BANGLADESH J CHILD HEALTH 2019; VOL 43 (3) : 174-176

Case Reports

Tyrosinemia Type 1 – A case report

FAHMIDA ISLAM[1], WAHIDUZZAMAN MAZUMDER[2], A.S.M. BAZLUL KARIM[3], SUBIR ANANDA BISWAS[4], RAFIA RASHID[5], MOHAMMAD SHARIFUL HASAN[6], FAHMIDA BEGUM[7]

Abstract

Tyrosinemia Type 1 is a rare inherited metabolic disorder attributable to a deficiency of enzyme fumaryl acetoacetate hydrolase. It has an autosomal recessive pattern of inheritance. It often presents with liver disease or liver failure with predominant bleeding tendencies, Fanconi syndrome and or rickets with neurological crisis. Diagnosis is based on clinical features, increased tyrosine and methionine in plasma and the presence of succinylacetone in urine. Untreated patient develops liver failure, cirrhosis and hepatocellular carcinoma and end stage of renal failure. Here we describe a 9 months old infant presented with massive ascites with hepatosplenomegaly, coagulopathy and hypoalbuminemia. The diagnosis of tyrosinemia type 1 was confirmed based on clinical and biochemical findings. We highlight the need for early diagnosis and initiating treatment at the earliest which improves the quality of life in these patients. Here we report a nine month old male infant presented with abdominal distension, hepatomegaly and ascities diagnosed as Tyrosinemia Type 1.

Keyword: *Tyrosinemia Type 1, inborn metabolic disease, autosomal recessive.*

Introduction

Tyrosinemia type 1 is an autosomal recessive inborn error of amino acid, tyrosine metabolism. The enzyme deficient is fumaryl acetoacetate hydrolase (FAH) coded by FAH gene that is located on chromosome 15q25.1.[1,2] The altered FAH gene produces an unstable or inactive enzymes, results in reduced or absent FAH activity which inturn in accumulation on fumaryl and malayl-acetoacetate causing cellular damage. Succinylacetone is derived from these metabolites is elevated in serum and urine of the patients. Tyrosinemia type 1 affects approximately 1 in 1,00,000 to 1,20,000 births.[3] The disorder is common in Quebec (1 in 16786 live births) and Scandinavia.[4] There have been few reports from India.[5,6] The patients with tyrosinemia die in the early year of their lives as a results of hepatic insufficiency. The literature reveals a markedly increased risk of hepatocellular carcinoma among the survivors.[7]

1. Assistant Professor, Shaheed Tajuddin Ahmad Medical College, Gazipur
2. Associate Professor, Pediatric Gastroenterology, BSMMU, Dhaka
3. Chairman and Professor, Pediatric Gastroenterology, BSMMU, Dhaka
4. MD Resident, Pediatric Gastroenterology, BSMMU, Dhaka
5. FCPS Student, Pediatric Gastroenterology, BSMMU, Dhaka
6. Medical Officer, Pediatric Gastroenterology, BSMMU, Dhaka
7. Assistant Professor, Pediatric Gastroenterology, BSMMU, Dhaka

Correspondence: Dr. Fahmida Islam, Assistant Professor, Shaheed Tajuddin Ahmad Medical College, Gazipur. cell no-01714097144, email: islam.fahmida@gmail.com

Received: 28/08/2018 **Accepted:** 23/05/2019

Case Summary

A 9 months old male infant, 2nd issue of non consanguineous parents, hailing from rural area got admitted with the complaints of abdominal distension for 20 days which was increasing day by day. He also developed high grade continued fever for 2 days, which was not associated with cough or any urinary problem. He had no history of jaundice, dark urine, pale stool, recurrent vomiting, early morning irritability, any sib death, family history of same type of illness, altered consciousness, convulsion and any bleeding manifestation. With these above complaints he was initially hospitalized in a medical college hospital and was treated with injectable and oral medications. As there was no significant improvement he was referred to our institution.

On examination, he was sick looking, afebrile, mildly pale, anicteric and there was no edema. Vital signs were within normal limit. Anthropometrically he was well thriving. On alimentary system examination, there was hepatosplenomegaly and ascites. Nervous

system and other systemic examination revealed normal findings.

The investigations performed were as follows: Haemoglobin 8.6 gm/dl, total leukocyte count 10500/cumm, differential count neutrophils 38%, lymphocytes 51%, monocytes 10%, and eosinophils 01%, Platelet count 95000/cmm, 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, SGPT-54 U/L with disproportionate liver synthetic dysfunction (albumin-23 gm/L and INR-2.8). The serum alpha-feto protein (AFP) levels were markedly raised (>30000ng/ml). Urine reducing substances were positive. TORCH screening was negative. Urine protein and creatinine ratio was normal. There was raised tyrosine and succinylacetone(1.2uM/L) level on blood tandem mass spectroscopy. An ultrasound study of the abdomen revealed normal liver size with coarse in echotexture with gross ascites with splenomegaly, both kidneys were increased in size and cortical echogenicity is increased. Liver biopsy could not be done because of coagulopathy. Urine succinylacetone(with TMS) was elevated. Serum electrolytes revealed hypokalemia (2.99 mmol/l). Serum LDH was 392 U/L.

The patient was advised with protein restricted diet and 2-(nitro-4-trifluoromethylbenzoyl) 1, 3cyclohexanedione (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

Tyrosinemia is an inborn error of tyrosine metabolism. Tyrosine is a semi essential amino acid, derived from the liberation of tyrosine from hydrolysis of dietary or tissue protein or from the hydroxylation of essential amino acid phenylalanine.[3] Hypertyrosinemia is of three distinct types. Tyrosinemia type 1 is due to the deficiency of the enzyme FAH and accumulation of toxic metabolites fumaryl acetoacetatewhich is hepatotoxic and maleyl acetoacetate is renal toxic. End product of fumaryl and maleyl acetoacetate is succinyl acetone. Presence of succinyl acetone in blood or urine are diagnostic for tyrosinemia type 1. Type 2, Reichner Hanhart Syndrome is caused by a deficiency of tyrosine aminotransferase which leads to the characteristic occulocutaneous syndrome. Type 2 tyrosinemia is due to deficiency of 4-hydroxypyruvate dioxygenase enzyme characterized by mental and motor retardation, seizures and intermittent ataxia.[8]

Tyrosinemia type 1 is characterized by progressive liver disease, renal tubular dysfunction, rickets, neurological crisis, hypertrophic cardiomyopathy etc. In acute type, hepatic insufficiency develops before six month of age as a result of micro and macronodular cirrhosis. Also presents as acute liver failure evidenced by coagulopathy with prolonged prothrombin time. Chronic type manifests itself with hepatomegaly, cirrhocis, rickets, growth retardation are observed after six months.[9] Most ominous in these patients is the risk of development hepatocellular carcinoma.

The increased level of serum tyrosine and methionine and urine succinyl acetone provide the key for diagnosis. Diagnosis is based on persistent ascites with hepatomegaly, disproportionate liver synthetic dysfunction with very high AFP levels. There is supportive published discussion that newborn screening using tendem mass spectrometry identification of succinyleacetone in newborn blood spots is the best current approach for early identification of hypertyrosinemia type 1.[10]

Conventional treatment is phenylalanine and tyrosine restricted diet and liver transplantation. Another treatment modality is the use of NTBC. Study documented that NTBC was a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase (HPD).[11] By blocking the proximal tyrosinemia pathway, NTBC minimizes the formation of fumaryl and maleylacetoacetate which documented the rapid reversal of clinical symptoms.[12] NTBC should be started as soon as the diagnosis of hypertyrosinemia type 1 is suspected either from newborn screening or clinical presentation. The recommended starting dose is 1 mg/kg/day. NTBC dosing should be sufficient to completely suppress plasma and urine succinylacetone detection and normalize liver and renal function. High level of tyrosine treated with NTBC have been associated with corneal disease. The current hypothesis is that crystalizes in corneal epithelial cells.[13]Therespone to NTBC is usually rapid, and urinary succinylacetone should normalize after 24 hours, with clinical response occurring within

one week. If there is no improvement or if the patient is in acute severe liver failure, the dose should be increased to 2 mg/kg.[14] If there is no response after about one week following NTBC therapy consideration for hepatic transplantation should be initiated.

Conclusion

It is important to diagnose Tyrosinemia Type 1 as early to prevent liver failure. Early treatment significantly alters the prognosis and provides the most favorable outcomes for the patients.

References

1. Kvittingen EA. Hereditary tyrosinemia type I – An overview. Scand J Clin Lab Invest Suppl. 1986;184:27-34.
2. FAH Gene: Genetics Home Reference. U.S. National Library of Medicine; c2000-01 Available from: http://www.ghr.nlm.nih. gov/gene/FAH. [Last updated on 2014 Nov 11; Last cited on 2014 Nov 12].
3. Mitchell G , Grompe M, Lambert M, Tanguay R. Hypertyrosinemia. In :Scriver CR, Beaudet AL, Sly WS, Valle D, edition. The Metabolic Basis of Inherited Disease.8th edition. New York: McGraw-Hill, 2000; 1777-1806.
4. De Braekeleer M and Larochelle J . Genetic epidemiology of hereditary tyrosinemia in Quebec and in Saguenay-Lac-St-Jean. American Journal of Human Genetics.1990; 47(2): 302-7.
5. VermaIC . Burden of genetic disorders in India. Indian Journal of Pediatrics.2000; 67(12): 893-8.
6. Karnik D, Thomas N, Eapen CE, Jana AK, Oommen A. Tyrosinemia type I: A clinico-laboratory case report. Indian Journal of Pediatrics.2004; 71(10): 929-32.
7. Croffie JM, Gupta SK, Chong SKF , Fitzgerald JF. Tyrosinemia Type 1 Should Be Suspected in Infants With Severe Coagulapathy Even in the Absence of other signs of Liver failure. Pediatrics 1999; 103 (3): 675-8.
8. Van Spronsen FT, Thomasse Y, Smit GP, Leonard JV, Clayton PT, Fidler V et al. Hereditary tyrosinemia type 1: A New clinical classification with difference in prognosis on dietary treatment. Hepatology 1994; 20 (5): 1187-90.
9. Grompe M. The pathophysiology and Treatment of Hereditary Tyrosinemia Type 1. Seminars in Liver Disease 2001; 21 (4): 563-71.
10. S tinton C, Geppert J, Freeman K, Clarke A, Fraser H, Sutcliffe P et al. Newborn screening for tyrosinemia type 1 using succinylacetone—a systematic review of test accuracy. Orphanet J Rare Dis 2017;12:48.
11. Santra S, Baumann U. Experience of nitisinone for the pharmacological treatment of hereditary tyrosinaemia type 1. Expert OpinPharmacother 2008;9:1229–36.
12. Lindstedt S, Holme E, Lock EA, Hjalmarson O, Strandvik B. Treatment of hereditary tyrosinaemia type I by inhibition of 4-hydroxyphenylpyruvate dioxygenase. Lancet 1992;340:813–7.
13. Michalski A, Leonard JV, Taylor DS. The eye and inherited metabolic disease: a review. J R Soc Med. 1988;81:286–90.
14. de Laet C, Dionisi-Vici C, Leonard JV,Mckieman P, Mitchell G, Monti L et al. Recommendations for the management of tyrosinaemia type 1. Orphanet J Rare Dis 2013;8:8.