

Hereditary tyrosinaemia type I presenting as multiple focal hepatic lesions

Bushra Afroze,¹ Zehra Fadoo,² Zabedah Mohammad Yunus³

Abstract

Hereditary tyrosinaemia type I is a devastating autosomal recessive metabolic disorder, which, if untreated, causes liver failure, rickets, painful neurological crisis and hepatocellular carcinoma. With the advent of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione, the outcome of hereditary tyrosinaemia type I has significantly improved; however this treatment is very expensive. For early diagnosis of hereditary tyrosinaemia type I, a high index of suspicion is required in children presenting with hepatomegaly, significantly raised alpha-fetoprotein and multiple focal hepatic masses. Children with untreated disease often succumb to the illness within the first 2 years of life.

Keywords: Tyrosinaemia type I, Focal hepatic lesion, Pakistani children.

Introduction

Hereditary tyrosinaemia type I (HT-I) (OMIM 276700) is a rare autosomal recessive disease caused by deficiency of fumarylacetoacetate hydrolase (FAH), which is the last enzyme in tyrosine catabolic pathway. This results in accumulation of toxic metabolites; maleylacetoacetate, fumarylacetoacetate, succinyl acetoacetate and succinylacetone, causing progressive hepatic and renal damage in untreated patients¹ Long-term complications of untreated HT-I is hepatic cirrhosis and hepatocellular carcinoma.²

Significant biochemical clues for diagnosis of HT-I are disproportionate deranged prothrombin time (PT) in the presence of normal or slightly raised alanine transaminase (ALT) and markedly elevated alpha-fetoprotein (AFP). Detection of excess of succinylacetone in biological body fluids of untreated patients is pathognomonic of HT-I.³ Measurement of FAH in cultured fibroblast or documentation of pathogenic mutation in FAH gene is the confirmatory test.

Cornerstone of medical treatment of HT-I is tyrosine and phenylalanine restricted diet plus 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC). NTBC is a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase,

and thus reduces tyrosine degradation and production of succinylacetone.⁴ Before NTBC, liver transplant (LT) was the curative treatment option for HT-I. Current indication for LT in HT-I is fulminant liver failure, decompensated chronic liver disease refractory to NTBC, hepatocellular carcinoma or poor protein tolerance.⁵

Children with untreated HT-I often present with failure to thrive and hepatomegaly. Liver impairment is progressive causing icterus, ascites and coagulopathy. Micro- and macronodular cirrhosis is present. Focal hepatic lesions on computed tomography (CT) scan of the liver are seen along with significantly raised AFP. These children are often considered to have hepatoblastoma and are subjected to liver biopsy. We describe two infants who presented with failure to thrive, hepatomegaly, significantly raised AFP and multiple focal hepatic lesions and were initially considered to have hepatoblastoma.

Case Report

Patient 1: A 10-month-old boy was initially seen by an oncologist. He was the fourth child of first-cousin parents, who noted him to have failure to thrive and progressive abdominal distension over one month duration. On examination, his weight was 7Kg (<5th percentile) and height was 72cm (on 25th percentile). He had clinical signs of rickets and hepatomegaly of 6cm below right costal margin and splenomegaly of 4cm in the long axis. His work-up included: AST 21 IU/L (normal <45); PT 17.8 seconds (control:11 seconds); international normalization ratio (INR) 1.74; alkaline phosphate 856 IU/L (normal :110-302); normal serum albumin, calcium and phosphorus with radiological evidence of rickets. CT scan of abdomen showed multiple hyperdense and hypodense well-defined lesions of variable size, scattered throughout the liver (Figure-1a). Differential diagnosis of neuroblastoma and hepatoblastoma was considered. Serum AFP and 24-hour urinary vanilmandelic acid (VMA) was done. Urinary VMA was normal and AFP was significantly raised at 60,189 IU/L (normal range for 1 month-1 year: 0.6-28.3). Considering hepatoblastoma, a liver biopsy was done which showed distorted hepatic parenchyma with steatosis but no evidence of hepatoblastoma.

At this point a metabolic disorder causing hepatosplenomegaly was considered and he was referred

^{1,2}Department of Paediatrics and Child Health, The Aga Khan University Hospital, Karachi, ³Institute Medical Research, Kuala Lumpur.

Correspondence: Bushra Afroze. Email: bushra.afroze@aku.edu

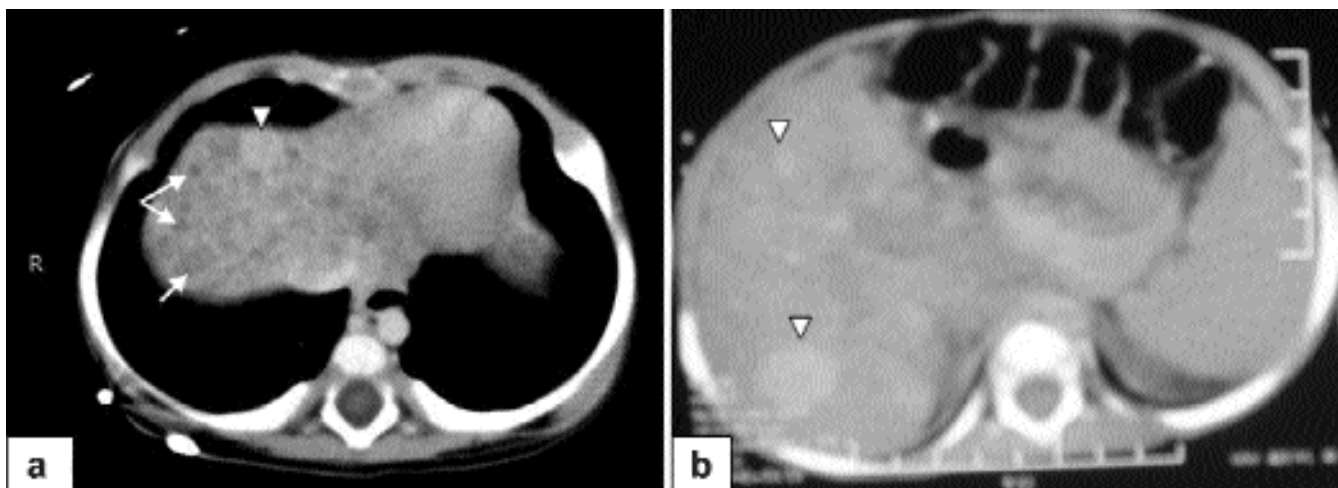


Figure-1: (Patient 1 - a) and (Patient 2 - b): CT scan of liver showing hyperdense well-defined lesions (white arrow heads) and multiple small hypodense lesions (white arrows) scattered throughout liver.

to the metabolic clinic. Mother volunteered information of his unpleasant body odour, which she described as "rotten vegetable smell". This critical information along with raised AFP, deranged PT in the presence of normal ALT lead to the diagnosis of HT-I. Urine organic acids were ordered and chromatogram showed 4 peaks of succinylacetone and 2 peaks of succinyl acetoacetate (Figure-2). Diagnosis of HT-I was confirmed by quantitative estimation of urinary succinylacetone, which was found to be 253mmol/mol creatinine (normal: 0.44 mmol/mol).

Parents were counselled about treatment options including tyrosine and phenylalanine restricted diet and NTBC, which they deferred due to high cost and were lost to follow-up.

Patient 2: He was the third child of first-cousin parents, who was noted to have failure to thrive and progressive abdominal distension secondary to hepatosplenomegaly starting at two months of age. He was evaluated by multiple general paediatricians, and many laboratory investigations were done including two CT scans of the abdomen but no diagnosis was reached.

He was first seen at the metabolic clinic at 8 months of age. His weight was 8Kg (<5th percentile) and height was 62cm (<5th percentile). Abdominal examination revealed hepatomegaly of 7cm below right costal margin and splenomegaly of 3cm in the long axis. Review of his laboratory results showed ALT 51 IU/L (normal<45), PT 19.4seconds (control: 11 seconds), INR 1.97, alkaline phosphatase 1142 IU/L (normal: 110-302), normal serum albumin, calcium and phosphorous. CT scan of the abdomen showed multiple hypodense well-defined lesions of variable sizes in both liver lobes. HT-I was clinically suspected, parents were counselled about possible diagnosis

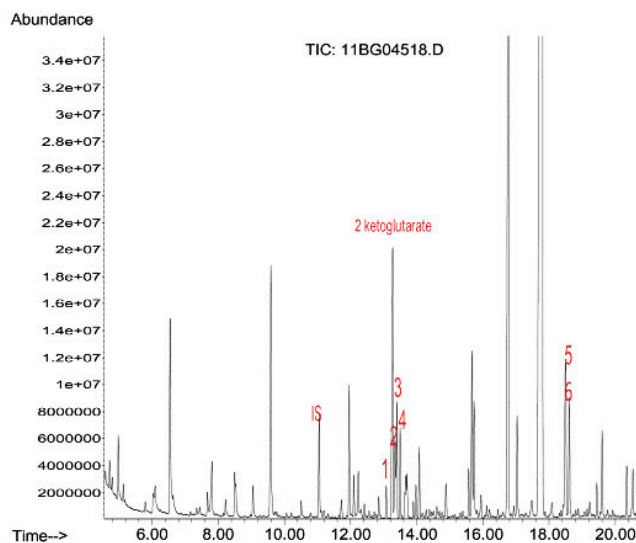


Figure-2: Urinary organic acids chromatogram of patient 1. Peak 1, 2, 3 and 4 are succinylacetone, peak 5 and 6 are succinyl acetoacetate. IS is internal standard (3,3-Dimethylglutaric acid).

and AFP was requested. Urine succinylacetone estimation was planned after AFP.

The patient was lost to follow-up for more than 5 months during which he visited multiple physicians and a third CT scan of the abdomen was done, which showed similar findings noted in previous CT scan. AFP was done at 1 year of age, which was 359,574 IU/L (normal range for 3months-1year: 0.6-28.3). Parents were given clinical diagnosis of hepatoblastoma and were advised for liver biopsy.

The patient was again brought to metabolic clinic at 1 year

of age. At that time he was very sick looking, weighed 6.3kg (<5th percentile on National Centre for Health Statistics (NCHS) growth charts) and abdominal cavity was almost completely occupied by the liver. After re-counselling of the parents, urine organic acids and urine for succinylacetone quantitative estimation was done. Urine organic acids chromatogram showed similar findings as Patient 1 and succinylacetone was 138 mmol/mol creatinine thus confirming diagnosis of HT-I. Parents were counselled about treatment options including tyrosine and phenylalanine restricted diet plus NTBC, which could not be arranged till writing of this manuscript due to high cost.

Discussion

Tyrosinaemia type I is a rare inherited metabolic disorder with a worldwide incidence of 1:100,000-1:120,000 with highest incidence in Scandinavia and Quebec, where the incidence is 1:20,000.⁶ In Pakistan the incidence of HT-I is not known. Less than 50% of patients with HT-I are diagnosed before death due to confusing clinical presentation,³ thus a high index of suspicion is required for timely diagnosis.

It is one of the few metabolic disorders with characteristic odour, which is described as "boiled cabbage" or "rotten mushroom" smell. "Rotten vegetable" odour was noted by the mother in the first patient, which helped in the diagnosis of HT-I. Biochemical clues for HT-I are normal or mildly elevated ALT, which is disproportionate to the degree of coagulopathy.⁷ Both patients had deranged PT in presence of normal or slightly raised ALT.

Alpha-fetoprotein was significantly raised in both patients and both were given clinical diagnosis of hepatoblastoma. It is known that AFP is a sensitive but not a specific marker for hepatocellular carcinoma.⁸ For children presenting with liver disease and markedly elevated AFP, HT-I should be considered in differential diagnosis.

Confirmatory pathognomonic metabolite for HT-I is detection of excess of succinylacetone in urine or plasma, which is typically detected by gas chromatography/mass spectroscopy. Clinicians may have to specially request for succinylacetone, so that selective ion monitoring is incorporated into the laboratory analysis for its detection.

Neurological crisis resembling acute intermittent porphyria is reported in 42% of patients^[9] resulting in death in 10% cases.¹⁰ This occurs secondary to excess of succinylacetone and succinyl acetoacetate, which inhibits d-aminolevulinic acid dehydratase, first enzyme in haem biosynthesis. None

of the patients described experienced neurological crisis.

Survival patients with HT-I have improved radically with use of NTBC, which is recommended in dose of 1 mg/kg/day in two divided doses¹¹ along with tyrosine and phenylalanine restricted formula. Both are expensive and are effective only when used together. Treatment could not be commenced in both patients due to high cost. Average monthly cost of NTBC for a 10kg child is US\$3825, which increases with weight and is required life-long. Cost of tyrosine and phenylalanine restricted formula, though much less than NTBC, adds to the accumulative treatment cost. Few centres consider LT as a treatment option in HT-I due to high cost of medical treatment.¹² Liver transplant has its own limitation; first of all, it is also an expensive treatment option. Secondly, after LT patients often require life-long immunosuppression medication. Unfortunately, LT is not performed for children in Pakistan and was thus also not done for either of the patients.

Conclusion

Expensive treatment options which are beyond the reach of most Pakistanis makes a cause for antenatal diagnosis of HT-I for couples at risk of having children with HT-I. Antenatal diagnosis can be done by mutation analysis FAH gene on chorionic villus sampling or amniocyte samples.

References

1. Chapkarani A, Holme E. Disorders of tyrosine metabolism. In: Fernandes J, Saudubray J, van den Berghe G, Walter J (eds). *Inborn Metabolic Diseases: Diagnosis and Treatment*. 4th ed. New York, NY: Springer; 2006; pp 233-43.
2. Scott CR. The genetic tyrosinemas. *Am J Med Genet C Semin Med Genet*. 2006; 142C: 121-6.
3. 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.
4. McKiernan PJ. Nitisinone in the treatment of hereditary tyrosinaemia type 1. *Drugs* 2006; 66: 743-50.
5. De Braekeleer M, Larochelle J. Genetic epidemiology of hereditary tyrosinemia in Quebec and in Saguenay-Lac-St-Jean. *Am J Hum Genet* 1990; 47: 302-7.
6. Croffie JM, Gupta SK, Chong SKF, Fitzgerald JF. Tyrosinemia type 1 should be suspected in infants with severe coagulopathy even in the absence of other signs of liver failure. *Pediatrics* 1999; 103: 675-8.
7. Holme E, Lindstedt S. Nontransplant treatment of tyrosinemia. *Clin Liver Dis* 2000; 4: 805-14.
8. Mitchell G, Larochelle J, Lambert M, Michaud J, Grenier A, Ogier H, et al. Neurologic crises in hereditary tyrosinemia. *N Engl J Med* 1990; 322: 432-7.
9. Holme E. Disorders of tyrosine degradation. In: Blau N, Hoffmann GF, Leonard J, Clarke JTR (eds). *Physician's Guide to the Treatment and Follow-up of Metabolic Diseases*. New York: Springer; 2006; pp 49-56.
10. El-Karaksy HM, Fahmy M, El-Raziky M, El-Koofy N, El-Sayed R, Rashed MS, et al. Hereditary tyrosinemia type 1 from a single center in Egypt: clinical study of 22 cases. *World J Pediatr* 2011; 7: 224-31.