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Case Report

Biochemical and molecular diagnosis of tyrosinemia type I with two novel *FAH* mutations in a Hong Kong chinese patient: Recommendation for expanded newborn screening in Hong Kong

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ABSTRACT

Objectives: Tyrosinemia type I is an autosomal recessive disorder in tyrosine metabolism. In areas without expanded newborn screening, patients present with acute hepatorenal failure in early infancy. Diagnosis can be elusive when clinical presentation is non-specific and biochemical abnormalities are masked by secondary changes. This is the first Hong Kong Chinese report.

Design and methods: A two-month-old Chinese male infant with unremarkable antenatal and postnatal history presented with progressive abdominal distension for three days. He suffered from end-stage liver failure, hypoglycemia and hepatic encephalopathy. Diagnostic work-up was complicated starting from rule-out sepsis, intestinal obstruction, volvulus, peritonitis, septic ileus, poisoning to metabolic diseases. Clinical, biochemical and genetic data was described.

Results: The patient showed increases in multiple plasma amino acids including tyrosine, phenylalanine and methionine, and hyper-excretions of 4-hydroxyphenyl-acetate, -pyruvate, and -lactate, as well as N-acetyltyrosine which could be seen in liver failure due to both tyrosinemia type I and non-metabolic conditions. Because of the volatile nature, succinylacetone was almost undetectable. The diagnosis was confirmed by genetic analysis of *FAH* with two novel mutations, viz. NM_000137.2:c.1063-1G>A and NM_000137.2:c.1035_1037del. Living-related liver transplantation was done. However, the patient still suffered many complications after the severe metabolic insult with hypoxic ischemic encephalopathy, cerebral atrophy, global developmental delay and cortical visual impairment.

Conclusions: Because of the lack of expanded newborn screening in Hong Kong, this child unfortunately presented in the most severe form of tyrosinemia type I. Expanded newborn screening can save life and reduce the burden of diagnostic complexity. This illustrates the need for expanded newborn screening in Hong Kong.

Introduction

Tyrosinemia type I (MIM #276700), one of the best documented inborn errors of metabolism (IEM), is an autosomal recessive disorder of fumarylacetoacetate hydrolase deficiency in the last step of tyrosine catabolism [1]. The metabolic pathway of tyrosine degradation involves five enzymes (Fig. 1), which are only expressed in liver and kidney. Tyrosine is metabolized into fumaric and acetoacetate which then enter into the Krebs cycle for energy production. In tyrosinemia type I, the enzymatic defect is the fumarylacetoacetase, leading to accumulation of toxic metabolites mainly fumarylacetoacetate and maleylacetoacetate. These metabolites are reduced to succinylacetoacetate and then decarboxylated to succinylacetone. Elevated succinylacetone in plasma and urine is pathognomonic. In addition, tyrosinemia type I is associated with a partial deficiency of 4-hydroxyphenylpyruvate oxidase which leads to elevated 4-hydroxyphenyl-pyruvate, -lactate and -acetate. Patients could have neurological symptoms resembling acute intermittent porphyria. It is due to the inhibitory effect of succinylacetone on delta-aminolevulinic dehydratase leading to elevated delta-aminolevulinate [2].

Tyrosinemia is perhaps a misnomer for this disorder because the enzyme deficiency itself does not directly lead to hypertyrosinemia. Instead, the accumulation of fumarylacetoacetate, maleylacetoacetate, succinylacetoacetate and succinylacetone, the elevated organic acids, leads to hepatorenal toxicity. The common findings of elevated plasma tyrosine, phenylalanine and methionine are non-specific secondary changes associated with liver damage.

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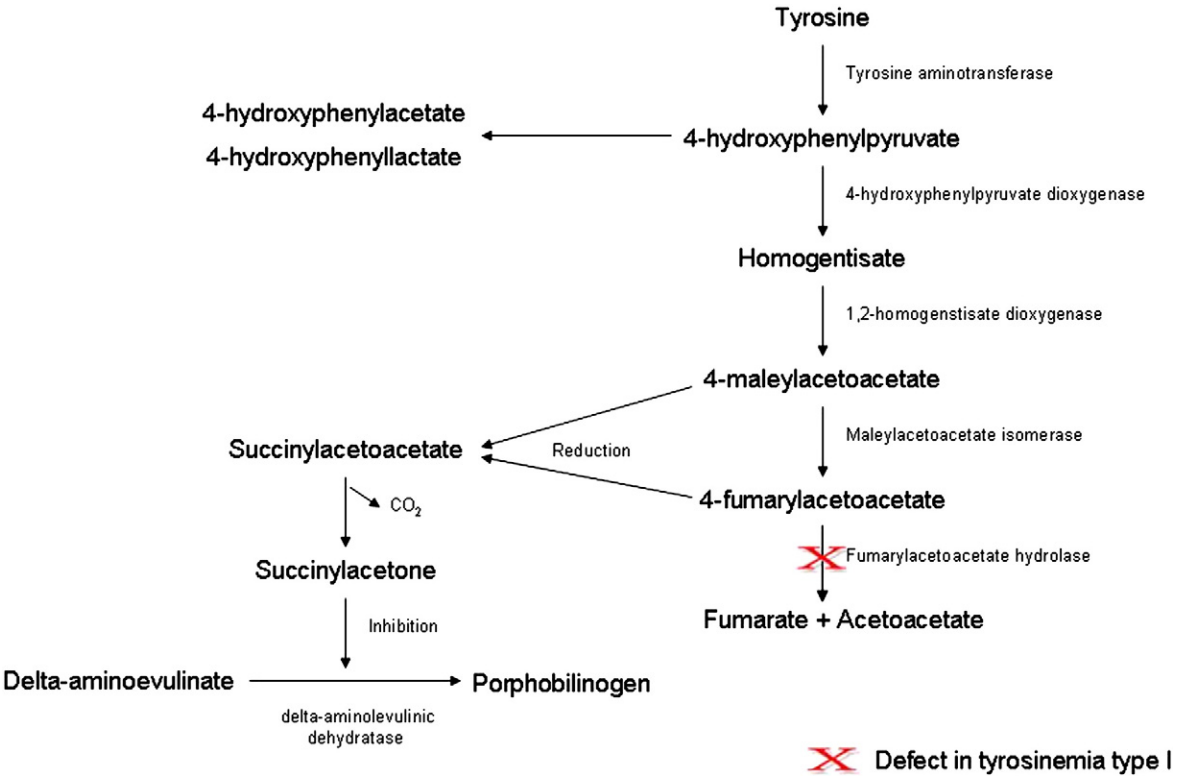

Fig. 1. Tyrosine metabolism pathway.

The corresponding gene, *FAH*, in chromosome 15q25.1, encodes 419 amino acids and is composed of 14 coding exons. There are only 71 disease-causing mutations reported so far on HGMD® Professional 2012.2 (accessed on 19 July 2012).

In areas without expanded newborn screening, patients present with acute and severe hepatorenal failure in early infancy. Patients who survive develop cirrhosis and hepatocellular carcinoma. Other uncommon clinical presentations include neurologic crisis of painful peripheral neuropathy, Fanconi syndrome, hypophosphatemic rickets, pancreatic islet cell hypertrophy-related hypoglycemia, and hypertrophic cardiomyopathy.

The justifications of expanded newborn screening program are mainly based on the adequate understanding of the disease nature, availability of a reliable and accurate screening test, and presence of an efficacious treatment [3]. NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione, nitisinone) is a very effective treatment for tyrosinemia type I [4,5]. This triketone compound which was previously developed as an herbicide is a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase avoiding the accumulation of toxic downstream metabolites. NTBC together with dietary restriction are effective treatment for tyrosinemia type I. Otherwise, liver transplantation remains another curative option.

Incidence of tyrosinemia is around 1 in 100,000 births worldwide [1]. With the advent of tandem-mass-spectrometry-laden expanded newborn screening, tyrosinemia type I is included as a mandatory national screening program in many countries. In Hong Kong where there is no expanded newborn screening, diagnosis of these patients still relies heavily on clinical suspicion and downstream investigations. Prognosis is definitely jeopardized in patients with late and severe presentations. We give the first report of a Hong Kong Chinese patient with tyrosinemia type I who presented late with end stage liver failure at two months old. Two novel mutations are described.

Case description

A two-month-old Chinese boy presented with progressive abdominal distension for three days. He also had fever, lethargy and cold extremities on admission. He was born full term by normal spontaneous delivery. The parents were non-consanguineous. Mother had maternal impaired glucose tolerance and the antenatal and postnatal histories were otherwise unremarkable. On physical examination, blood pressure was 90/37 mm Hg (reference interval (RI): 45–85) with pulse 128/min (RI: 100–150). The capillary refill took 3 s indicating no significant decrease in peripheral perfusion. He had tachypnea and insucking chest with occasional grunting. The abdomen was grossly distended with sluggish bowel sounds. His liver function tests showed a serious liver failure with a cell burnout picture, alanine transaminase 41 IU/L (RI: <56) and aspartate transaminase 55 IU/L (RI: <77), alkaline phosphatase 1505 IU/L (RI: 82–383), total bilirubin 40 μmol/L (RI: <21), albumin 16 g/L (RI: 28–46), and prolonged clotting profile with INR 6.75. His hemoglobin was 9 g/dL (RI: 10.0–20.5) and platelet count was 71×10^9/L (RI: 210–650). He had hypoglycemia with lowest plasma glucose of 0.6 mmol/L. Abdominal X-ray showed dilated bowels without free gas or fluid level.

He was managed as intra-abdominal sepsis with septic shock and liver failure. The possible causes included intestinal obstruction, malrotation or volvulus, primary peritonitis and septic ileus. Poisoning and metabolic conditions were also considered because of the liver failure. Empirical antibiotics were given and blood culture yielded *Enterobacter cloacae*.

The patient's condition deteriorated and required mechanical ventilation with inotropic support. More extensive investigations were followed. Echocardiogram showed good contractility with no pericardial effusion. Contrast meal and follow through showed no malrotation or intestinal obstruction. Ultrasonography indicated the presence of ascites and some fluid filled bowel loops. The liver was normal in size with no obvious hepatic lesion. The biliary tree was not dilated. Computer tomography of the abdomen suggested no gross inflammatory changes at the right lower quadrant but with features of colitis. Erythema and induration were noted over the right lower quadrant of his abdomen. Exploratory laparoscopy was performed for the possibility of intra-abdominal loculation or abscess. It was found to have ascites with fibrinous material in the right lower quadrant and a congested appendix. Laparoscopic appendectomy was