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Journal of Endocrinology and Disorders
Shang Xiaohong*

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Review Article

A Case Report of Hereditary Tyrosinemia type I

Shang Xiaohong[1,3,4*], Shao Meng[2], Wang Zengmin [1,3,4], Wang Fengxue [1,3,4], Li Guimei [1,3,4]

[1] Department of Pediatic Endocrinology, Shandong Provincial Hospital, Jinan 250000, China.

[2] Department of Pediatic, Huantai County maternal and child health Hospital, Zibo City, Shandong Province, 25500, China.

[3] Department of Pediatic Endocrinology, Shandong Provincial Hospital Affilated to Shandong First Medical University, Jinan 250000, China.

[4] Department of Pediatic Endocrinology, Shandong Provincial Clinical Research Center for Childrens Health and Disease office, Jinan 250000, China.

***Corresponding Author:** Shang Xiaohong, Department of Pediatic Endocrinology,Shandong Provincial Hospital, Jinan 250000, China.

Received Date: 03 December 2024 | Accepted Date: 16 December 2024 | Published DATE: 15 January 2024

Citation: Shang Xiaohong, Shao Meng, Wang Zengmin4 Wang Fengxue, Li Guimei (2025), A case report of hereditary tyrosinemia type I, *J. Endocrinology and Disorders*, 9(1): DOI:**10.31579/2640-1045/168**

Abstract

Summary of case history: Patient is a 3-year-old female and was first diagnosed on September 1st, 2020 (postnatal day 20) due to lasting high tyrosine level detected for 11 consecutive days.

Symptoms and signs: Patient did not exhibit jaundice, hemorrhage, or ascites. Physical examinations did not show any obvious abnormality.

Diagnostic methods: Neonatal hereditary and metabolic disease screening was performed and found high tyrosine level, surmising tyrosinemia. Further urine organic acid analyses showed increased levels of succinylacetone (SA), 4-Hydroxyphenylacetic acid, 4-hydroxyphenyllactic acid, and 4-Hydroxyphenylpyruvic acid. Additional blood tests found high levels of alpha-fetoprotein (AFP), serum ammonia, serum lactate, alkaline phosphatase (ALP), and bile acid, reduced hemoglobin and serum phosphorus, and normal levels of alanine transaminase (ALT), glucose, and creatine. Genetic testing found a pathogenic FAH c.553+1G>A homozygous variant in the proband. Parents of the proband carried the same heterozygous variant at this locus. Thus, the patient was diagnosed as hereditary tyrosinemia type I (HT-1).

Therapeutic methods: Low tyrosine and phenylalanine diet was given. Phosphate mixture and ursodeoxycholic acid (UDCA) were administered to supplement phosphorus and enhance cholagogue, respectively. Additional therapies aimed to correct anemia and replenish calcium. However, patient's condition was not well controlled.

Clinical outcomes: Anemia and hypophosphatemia shown in the patient were not improved. Under monitoring, high levels of AFP still lasted. Physical examination did not show unusual observations. Parents of the patient were referred and advised to consult about liver transplantation at higher level hospitals.

Keywords: hereditary tyrosinemia; succinylacetone;nitticinone; liver

Introduction

Transplantation Hereditary Tyrosinemia Type I (HT-1) is a genetic metabolic disorder caused by a deficiency in the final enzyme, fumarylacetoacetate hydrolase, in the tyrosine metabolism pathway. It's an autosomal recessive inheritance with a global incidence of approximately 1/120,000 to 1/100,000, showing significant ethnic and regional differences. The disease's main clinical manifestations include progressive liver damage, renal tubular dysfunction, and acute intermittent porphyria-like neuropsychiatric symptoms. Currently, nitisinone and liver transplantation are considered optimal treatments. This article reports on a case of a child with HT-1, initially detected through newborn screening, and aims to enhance clinicians' understanding of the disease and the necessity of newborn metabolic disease screening.

The patient, diagnosed with Hereditary Tyrosinemia Type I, first sought medical attention at 20 days old due to elevated tyrosine levels detected 11 days earlier. By the last consultation at the age of 1 year and 4 months, the child showed no signs of jaundice, bleeding, or ascites, and their growth and development were largely normal. Throughout this period, the patient had multiple follow-up visits with no significant abnormalities found in physical examinations. The treatment included a low-tyrosine and phenylalanine diet, phosphate supplements, bile aids, iron, and calcium. There has been no follow-up since December 13, 2021. The

patient's past medical history, personal history, and family history were unremarkable.

After the newborn screening, genetic testing revealed a homozygous mutation (c.553+1G>A) in the FAH gene, identified as a pathogenic variant. Both parents were carriers of this mutation, being heterozygous at the same site. An echocardiogram showed an unclosed oval foramen in the heart. Due to personal reasons of the patient's parents, an abdominal ultrasound, recommended to assess potential liver and kidney enlargement, was not conducted at the hospital. Consequently, the extent of any liver or kidney enlargement remains unclear.

The diagnosis of HT-1 for the patient was confirmed based on elevated blood tyrosine levels, increased urinary succinylacetone (SA), 4-hydroxyphenylacetic acid, 4-hydroxyphenyllactic acid, and 4-hydroxyphenylpyruvic acid. Genetic testing revealed a homozygous mutation in the FAH gene (c.553+1G>A). Additionally, the patient's clinical symptoms included anemia, hypophosphatemia, significantly elevated alpha-fetoprotein, and increased blood ammonia and lactate levels. While the initial screening and urinary organic acid analysis did not rule out Tyrosinemia Type II or III, genetic testing confirmed the diagnosis of HT-1 and excluded these other types.

From 20 days after birth, the patient was placed on a low tyrosine and low phenylalanine diet. At the age of 1 year and 1 month, the patient developed moderate anemia, significantly increased alkaline phosphatase, and elevated bile acids, leading to the addition of medications like iron supplements, vitamin D2 phosphate calcium tablets, and ursodeoxycholic acid. By 1 year and 4 months, continued low blood phosphate levels were treated with phosphate supplements. The patient's parents were advised to consult about liver transplantation at a higher-level hospital. As of a follow-up call on June 9, 2022, the patient had not undergone liver transplantation or started nitisinone treatment, continuing with dietary and symptomatic treatments, with reportedly satisfactory test results. Specific details were not disclosed by the parents.

The patient, treated with a low tyrosine and phenylalanine diet, phosphate supplements, iron supplements, vitamin D2 phosphate calcium tablets, and ursodeoxycholic acid, showed no signs of jaundice, bleeding, or rickets at the last visit. As of August 30, 2023, multiple phone follow-ups indicated that the child was doing well according to the parents, who declined to provide further details on tests and treatments and were not considering an imminent follow-up appointment.

Tyrosinemia can be divided into Types I, II, and III, based on defects in different enzymes in the metabolic pathway. Type I, also known as hepatorenal tyrosinemia, is mainly caused by a defect in the fumarylacetoacetate hydrolase enzyme in liver and kidney tissues, leading to a tyrosine metabolism disorder and insufficient development of 4-hydroxyphenylpyruvic acid dioxygenase in the liver. During this, maleylacetoacetate and fumarylacetoacetate cannot be metabolized normally, instead producing succinylacetoacetate and SA through an alternate metabolic pathway, which become the main toxic intermediate metabolites. This type is characterized by progressive liver damage, renal tubular dysfunction, and acute intermittent porphyria-like neuropsychiatric symptoms. Type II Tyrosinemia, known as oculocutaneous tyrosinemia, is caused by a deficiency of tyrosine transaminase, leading to corneal thickening, palmoplantar keratosis, and developmental delays. Type III, which is rarer, results from a deficiency in 4-hydroxyphenylpyruvate dioxygenase, with uncertain clinical manifestations. HT-1 has the highest incidence rate among them. This article reports a case of Type I Tyrosinemia.

Based on the onset and clinical manifestations, HT-1 can be classified into acute (usually occurring within two months of birth), subacute (between two and six months of age), and chronic types (appearing after six months of age). The acute type, most common, presents similarly to neonatal hepatitis syndrome, with symptoms like jaundice, anemia, hypoglycemia, coagulation abnormalities, ascites, hepatosplenomegaly, cirrhosis, and sometimes hyperinsulinemia. Some cases also report thrombocytopenic purpura. The subacute type shares similar manifestations with additional growth and developmental delays and hypophosphatemic rickets, progressing quickly. The chronic type progresses more slowly and is characterized by growth retardation, progressive liver cirrhosis, renal tubular dysfunction, manifesting as hypophosphatemic rickets, diabetes, proteinuria, and aminoaciduria (Fanconi syndrome), with some patients developing liver tumors. About 40% of patients may experience acute peripheral neuropathy crises. All types have a significantly increased risk of hepatocellular carcinoma, occurring earlier than in the general population. Untreated patients surviving early acute liver failure have a 40% chance of developing hepatocellular carcinoma after age two. Some patients also have hypertrophic cardiomyopathy.

The diagnosis of HT-1 relies on a comprehensive analysis of clinical presentations, biochemical tests, and genetic testing. Elevated levels of urinary SA are a specific marker for HT-1, constituting a crucial biochemical diagnostic basis. However, cases of HT-1 without increased SA and persistent elevated SA levels due to GSTZ1 mutation (not FAH mutation) have been reported. Molecular genetic testing, identifying biallelic mutations in the FAH gene, is a reliable method for confirming HT-1 diagnosis. The FAH gene has over 100 reported pathogenic mutations globally, with ethnic-specific hotspot mutations. In addition to genetic testing, urinary organic acid analysis often shows increased tyrosine metabolites and amino acid testing reveals elevated tyrosine levels, potentially accompanied by increased methionine and phenylalanine. Some patients may develop hypergalactosemia. Clinically, significant increases in serum alpha-fetoprotein, coagulation abnormalities, elongated prothrombin time, and activated partial thromboplastin time, with mild to moderate increases or normal levels of transaminases and bilirubin are common. Decreased blood phosphate and blood sugar levels, increased alkaline phosphatase, and urine tests showing glycosuria and proteinuria are observed. Blood tests may reveal anemia and thrombocytopenia. Abdominal ultrasound aids in early detection of hepatic cancer changes and renal structural alterations. Newborn screening is crucial for early detection of asymptomatic HT-1 patients, and with improved diagnostic capabilities in China, reports of HT-1 are increasing. However, elevated tyrosine levels are also common in transient neonatal tyrosinemia, lacking diagnostic specificity. The child in the case study was first identified with elevated tyrosine levels during newborn metabolic disease screening. Subsequent urine organic acid analysis showed increased levels of SA and other tyrosine metabolites. Clinical examination revealed anemia, lowered blood phosphate, and significantly elevated alpha-fetoprotein. Genetic testing confirmed a homozygous mutation in the FAH gene (c.553+1G>A), classified as pathogenic according to ACMG guidelines. Hence, the diagnosis of HT-1 for this child was clear.

Restricting the intake of tyrosine and phenylalanine in the diet was the main treatment for HT-1 before the 1990s. The current dietary treatment principle is to restrict the intake of natural protein to maintain blood amino acid levels within a relatively suitable range, while supplementing with special medical food formulas free of tyrosine and phenylalanine to meet the growth and development needs of affected children. The ideal control range for blood tyrosine is 200 to 400 μmol/L or 200 to 600 μmol/L, and blood phenylalanine should be maintained within the normal range [25,26]. For children with hypophosphatemia, oral administration of compound phosphate salts and vitamin D3 can normalize blood phosphate levels. In 1992, nitisinone was introduced as a specific drug for the treatment of HT-1. This drug inhibits the activity of recombinant human 4-hydroxyphenylpyruvate dioxygenase (4HPPD) and blocks the proximal tyrosine metabolic pathway, effectively reducing the production of SA and rapidly reversing the clinical symptoms of children with HT-1 [27], significantly reducing the incidence of hepatocellular carcinoma, but the treatment effect is closely related to the timing of initiation [3]. Since nitisinone can further increase the concentration of tyrosine in the body, it is necessary to combine it with a low-tyrosine diet to prevent complications such as corneal clouding and palmoplantar keratoderma.

Combined treatment with nitisinone and diet can promote long-term survival in children. In cases where nitisinone treatment is not possible, living donor liver transplantation is currently a better option for affected children in our country [1]. There have been several cases in the country where living donor liver transplantation has been used to treat HT-1, with children showing normalization of tyrosine metabolism, significant reduction in abnormal metabolic products, and good catch-up growth post-transplantation [20, 28]. Liver transplantation surgery carries certain risks, and after transplantation, lifelong immunosuppressants are required along with regular follow-up, and the long-term prognosis is still unclear. Ribes Koninckx and others [29] performed hepatocyte transplantation for a child with HT-1 who developed coagulation dysfunction during nitisinone treatment, with postoperative improvement in biochemical indicators and clinical symptoms, making this method a promising and effective treatment option. Currently, numerous gene therapy trials have been conducted on animal models, including ex vivo and in vivo gene therapies, all achieving good therapeutic effects [30-33]. Additionally, enzyme replacement therapy is also in a rapid research phase. For untreated children with HT-1, the overall prognosis is poor. The 2-year survival rate for children with acute HT-1 is only 29%, with the main causes of death being acute liver failure and recurrent bleeding. For children with subacute HT-1, the 2-year survival rate is about 74%, and the 5-year survival rate is about 30%, with the main causes of death being hepatocellular carcinoma and liver failure. Children with chronic HT-1 have a slower disease progression, with a 2-year survival rate of about 96% and a 5-year survival rate of about 60%. The main causes of death in these cases are hepatocellular carcinoma and neurological crises [2,25]. This case involves a child with anemia and hypophosphatemia, with a significant increase in alpha-fetoprotein levels. Currently, the child is only receiving dietary restrictions and symptomatic drug treatment, without nitisinone or liver transplantation treatment. The inability of the parents to bring the child for regular follow-up due to personal reasons increases the risk of sudden liver failure and major bleeding, leading to a high probability of a poor prognosis.

The overall incidence of HT-1 is quite low, making newborn metabolic disease screening crucial for early detection of asymptomatic cases. Biochemical blood tests, blood amino acid analysis, and urine organic acid analysis are helpful for diagnosis, with molecular genetic testing being the gold standard. HT-1 is a treatable genetic metabolic disease; besides dietary restriction and symptomatic treatment, nitisinone and liver transplantation show significant efficacy. With nitisinone available in China, it's hoped to gain more experience in drug treatment and research. Liver cell transplantation might become a viable alternative due to limitations in liver source availability for transplantation. Enzyme replacement and gene therapy are still under research, with hopes that medical advancements will improve the lives of HT-1 patients.

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DOI:10.31579/2640-1045/171