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Tyrosinemia Type III: A Case Report with a Seven Years Follow-up

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Abstract

Hereditary tyrosinemia type III (OMIM 276710) is a rare inborn error of tyrosine metabolism caused by the deficiency of 4-hydroxyphenylpyruvate dioxygenase (HPD). This metabolic statement is transmitted in an autosomal recessive trait and hitherto about 18 cases presenting with this disease have been reported in the literature. Because of the low prevalence of the disease, the clinical phenotype remains variable and unclear, but the main symptoms are mostly related to the high concentrations of tyrosine and phenolic metabolites, namely mental retardation, ataxia, and seizures. We described the clinical, biochemical, and molecular characteristics of an Iranian female patient with tyrosinemia type III and her 7-year follow-up plan. A novel variant of HPD (609695) mutation (c.759+1 G>A) was identified in a homozygous pattern. Despite not being compliant with the recommended diet, the patient continued to have normal neuropsychiatric development in the follow-up, which questions the efficacy of a low-tyrosine diet.

***Key Words*:** Child, HPD gene, Tyrosinemia type III, Tyrosine metabolism.

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1- INTRODUCTION

Tyrosine is an essential amino acid in producing thyroid hormones, melanin, and catecholamines, which is derived from the hydroxylation of phenylalanine. The catabolic pathway of tyrosine consists of five steps and three autosomal recessive diseases, i.e. tyrosinemia type I, II, and III, result from the impairment of different enzymes in this pathway, which leads to elevated serum tyrosine concentrations (1, 2). Tyrosinemia type III is an autosomal recessive disorder caused by a deficiency in the activity of HPD and is characterized by elevated levels of blood tyrosine and massive excretion of its derivatives into the urine, including 4-hydroxyphenylpyruvic acid, 4-hydroxyphenyllactic acid, and 4-hydroxyphenylacetic acid (3). This type of hereditary tyrosinemia is rare and only a few numbers of cases have been reported globally (4). Patients with this disorder have been reported to show a wide range of neurological symptoms, from mild mental retardation and/or convulsions to autism and intellectual disabilities, with the absence of liver damage.

On the other hand, some studies report cases of tyrosinemia type III with normal development and intelligence, which shows the high variability of symptoms in this disorder ranging from asymptomatic in patients identified through screening studies to those with neurologic manifestations (5, 6). Herein, we report a detailed case of Tyrosinemia type III in Iran due to a novel homozygous likely-pathogenic mutation (c.759+1 G>A) in an asymptomatic female patient with elevated levels of plasma tyrosine.

2- CASE PRESENTATION

The index case is an 8-year-old Iranian female with normal mental and psychomotor development without neurological symptoms. She was born at full term with a birth weight of 3.120 g and a birth length of 49 cm. Regarding the family history, there were some cases of metabolic diseases among family members, thus this patient was referred to perform screening for the metabolic panel. Our patient is an offspring of consanguineous parents and has one normal sibling. In January 2014, the patient was referred to the pediatric metabolic and endocrinology clinic, Mashhad, Iran, for screening and counseling at 1 year of age and was then followed up every 6 months since 2014.

The values of height (83 cm, 42.8% percentile, Z-score: -0.18), weight (13 kg, Z-score: 1.01), serum tyrosine level (633 µmol/L, normal range: 10-145), and serum phenylalanine level (28 µmol/L, normal range: 32-85) were measured in the patient. Biochemical and metabolic test results are gathered in **Table.1**. Laboratory findings and biochemical abnormalities were suggestive of hereditary tyrosinemia. Confirmation of the diagnosis was obtained by a genetic analysis using the whole-exome sequencing test, which demonstrated a homozygous mutation in intron 10, c.759+1 G > A in the HPD gene, which is the likely-pathogenic mutation for Tyrosinemia type III.

Table-1: Laboratory findings of the target patient in her first visit (2012).

Test	Result (Unit)	Normal Range (Unit)
WBC count	12.23 (1000/µL)	5.7 - 16.3 (1000/µL)
Hemoglobin	13.0 (g/dL)	12.3 – 15.3 (g/dL)
Platelet count	225 (1000/µL)	150-450 (1000/µL)
BUN	8 (mg/dL)	7 – 23.5 (mg/dL)
Creatinine	0.3 (mg/dL)	0.5- 1.2 (mg/dL)

AST	49 (IU/L)	Up to 40 (IU/L)
ALT	11 (IU/L)	Up to 40 (IU/L)
Serum tyrosine	633 (µmol/L)	10 – 145 (µmol/L)
Serum phenylalanine	28 (µmol/L)	32 – 85 (µmol/L)
Urine hydroxyphenyllactic acid	Elevated	
Urine hydroxypyruvic acid	Elevated	
Urine succinylacetone	Normal	
AFP	5.43 (IU/mL)	Up to 8.5

WBC: White Blood Cell, BUN: Blood Urea Nitrogen, AST: Aspartate Transaminase, ALT: Alanine Transaminase, AFP: Alpha-fetoprotein.

Before revealing the type of hereditary tyrosinemia by genetic testing, the patient was asked to start a tyrosine-restricted diet and nitisinone for a short period since the prevalence of tyrosinemia type I seems to be higher among the population than the other two types. It is worth mentioning that after 2 weeks of starting the medication, the patient returned to the clinic due to adverse effects of nitisinone instead of feeling better. Thus, the medical team decided to stop the medication and wait for the genetic results. Eventually, the mutation in the HPD gene and classifying the presented tyrosinemia as type III confirmed the fact that nitisinone was not a suitable treatment for this patient. The protein intake was controlled using a special diet with low levels of tyrosine and phenylalanine while avoiding protein-rich foods. The patient's clinical presentation, serum tyrosine level, and hepatic enzymes have been evaluated annually since her first visit up to now. Fortunately, our patient never showed significant neurological symptoms and her performance in school is acceptable. Although the patient's compliance with the diet was low and her tyrosine levels fluctuated during the last 2 years of the follow-up (the findings of her last follow-up visit are shown in **Table.2**), there have been no clinical presentation and liver function tests have been within the normal ranges.

Table-2: Laboratory findings of the target patient in her last follow-up visit (2019).

Test	Result (Unit)	Normal Range (Unit)
Serum tyrosine	942.5 (µmol/L)	10 – 145 (µmol/L)
Serum phenylalanine	69.0 (µmol/L)	32 – 85 (µmol/L)
AST	34.5 (IU/L)	Up to 40 (IU/L)
ALT	16.8 (IU/L)	Up to 40 (IU/L)
AFP	1.1 (ng/mL)	Up to 8.5 (ng/mL)

AST: Aspartate Transaminase, ALT: Alanine Transaminase, AFP: Alpha-fetoprotein.

3- DISCUSSION

Tyrosinemia type III results from the malfunction of the HPD gene (encoding 4-HPPD), which is an essential enzyme in the tyrosine catabolism pathway. This enzyme is mainly expressed in neurons, neutrophils, kidneys, and liver cells thus the likely presentations of the disease are expected to involve the neurological system and functions of kidneys and liver. While there is not enough epidemiological data available regarding the exact prevalence of tyrosinemia type III, it is estimated that this is the rarest type of the three tyrosine metabolism disorders (7, 8). However, it is also suggested that the real prevalence might be higher among the

general population due to the existence of completely asymptomatic patients (9). The HPD gene is located at 12q24-qter, spans approximately a 21-kb genomic sequence, and contains 14 exons and 13 introns (9). Studies have shown many patients with neurodevelopmental manifestations, including intellectual impairment, learning difficulties, dyslexia, attention-deficit hyperactivity disorder (ADHD), behavioral disturbance, ataxia, microcephaly, hypotonia, and seizures, but no classical phenotype has been described for tyrosinemia type III (10).

Similar to our case, there have been asymptomatic patients with tyrosinemia type III who were identified only by genetic studies. This indicates the wide spectrum of presentations and the difficulty in the diagnosis of this genetic condition. The symptoms of tyrosinemia type III are not well specified yet, and there were no recognized correlations between serum tyrosine levels, the clinical presentation, and the mutation type in previous studies. There is no specific treatment available for patients with tyrosinemia type III, and the pathophysiology of neuronal injury is not fully understood in this disease.

However, previous studies have recommended treating patients with a restricted tyrosine- and -phenylalanine diet, especially in childhood, which might improve the long-term prognosis of the disease, although its efficacy is not proven yet (5, 10). Despite the diet recommendations given to the patient, our case did not have good compliance, which led to persistently high concentrations of serum tyrosine levels. In the long run, however, she did not develop neurodevelopmental or psychiatric symptoms related to tyrosinemia type III. This is in line with the findings of Edyta Szymanska et al. who showed that a tyrosine-restricted diet might not be indispensable for these patients (9).

4- CONCLUSION

We reported a case of asymptomatic tyrosinemia type III detected by screening for metabolic panel (due to positive family history of metabolic disorders), and confirmed it by a genetic analysis (which demonstrated a homozygous mutation in intron 10, c.759+1 G > A in the HPD gene). Despite the noncompliance with the recommended diet, she continued to have normal neuropsychiatric development in the 7-year follow-up, which emphasizes the need for future studies to better understand the pathophysiology of the disease and determine the efficacy of a low-tyrosine diet in altering its natural course.

5- CONFLICT OF INTEREST: None.

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