Tyrosinemia Type I and Reversible Neurogenic Crisis After a One-Month Interruption of Nitisinone

Havva Yazıcı1, Ebru Canda1, Esra Er1, Mehmet Arda Kılınç2, Sema Kalkan Uçar1, Bülent Karapınar2, Mahmut Çoker1

1Ege University Faculty of Medicine, Department of Pediatrics, Division of Pediatrics Metabolism and Nutrition, İzmir, Turkey
2Ege University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Intensive Care Unit, İzmir, Turkey

ABSTRACT

Hereditary tyrosinemia Type I (HTI) (OMIM 276700) is an autosomal recessive disorder due to a deficiency of the enzyme fumarylacetoacetate hydrolase. The liver is the primary organ that is affected and comorbidities with renal and neurologic systems and hepatocellular carcinoma can be seen as a long-term complication. An effective treatment has been available with 2-[2-nitro-4-trifluoromethylbenzoyl]-1,3-cyclohexanedione (NTBC) since 1992. Neurogenic crises do not take place in HTI patients who are treated with NTBC. Here, we report on a seven-year-old boy who underwent a severe neurological crisis including anorexia, vomiting, weakness, hyponatremia, paresthesia and paralysis of the extremities, seizure and arterial hypertension after an interruption of NTBC treatment. With the re-introduction of NTBC, the patient gradually reacquired normal neurological functions, normal blood pressure and recovered completely.

Keywords: Tyrosinemia Type I, neurogenic crises, nitisinone

Introduction

Hereditary tyrosinemia Type I (HTI) (OMIM 276700) is a rare inborn error of the tyrosine metabolism due to a deficiency of the enzyme fumarylacetoacetate (FAA) hydrolase in the tyrosine catabolic pathway (Figure 1) (1). Biochemically, patients typically have high tyrosinemia and toxic metabolites. Toxic metabolites and their derivates such as FAA, maleylacetoacetate, succinyl acetoacetate and succinyl acetone (SA) play a major role in tissue damage with hepatic, renal and neurological findings. Before 2-[2-nitro-4-trifluoromethylbenzoyl]-1,3-cyclohexanedione (NTBC), over 90% of patients died before 12 years of age 10% of them were due to neurogenic crises with respiratory problems (2). A L-phenylalanine and tyrosine restricted diet was the only treatment. The introduction of NTBC about 25 years ago greatly enhanced survey and prognosis of HTI as it was effective within hours, eradicating hepatic and neurological findings and protecting from the risk of hepatocellular carcinoma when treatment starts within the first months of life (3). NTBC had been used as a herbicide. The mechanism of NTBC is as an inhibitor of 4-hydroxyphenylpyruvate dioxygenaseis to block tyrosine catabolism at an initial step and convert HTI into Type III tyrosinemia. This hinders the production of toxic metabolites which are responsible for the hepatic, renal and neurological involvements of these toxic products, SA was discovered to curtail the activity of the enzyme delta 5-aminolevulinic acid dehydratase in the heme pathway (Figure 1). Thus, neurogenic crises in HTI have a physiological base fundamentally similar to those occurring in porphyria and lead poisoning, in which delta 5-aminolevulinic acid is also heightened. The clinical courses of these neurogenic crises also resemble Guillain-Barré syndrome. Porphrya-like syndrome is usually precipitated by an intercurrent infection or interruption of NTBC. These
crises with severe progression are characterized initially by pain (including abdominal pain resembling an acute surgical emergency), weakness and autonomic changes such as hypertension and hyponatremia. Patients may display an acute progressive ascending motor neuropathy, with or without hypertonic posturing, self-mutilation and convulsion. If this rarely seen complication is not diagnosed and treated early, it can be fatal. In a longitudinal study of HTI patients, no patient developed a neurogenic crises while being treated with NTBC (4). We report on a seven year-old boy with a severe neurological crisis including anorexia, vomiting, weakness, hyponatremia, paresthesia and paralysis of the extremities, seizure and arterial hypertension after a one-month interruption of NTBC treatment. The patient slowly regained normal neurological functions and normal blood pressure and recovered completely with the re-introduction of NTBC.

Case Report

A boy at the age of seven was referred to the emergency room with abdominal pain, vomiting and weakness. The child was born at term as a first child of non-consan-gineous parents with a normal birth weight and length. When he was eight months old, he had hepatosplenomegaly, rickets and hypotonia. He was diagnosed with HTI due to elevated plasma tyrosine and urine SA levels. The patient was immediately put on a restricted phenylalanine and tyrosine diet in conjunction with NTBC. Under this treatment by diet and NTBC (1-2 mg/kg/d), the boy developed normally until eight months and then ceased. At present, the patient continues diet and NTBC therapy.

Discussion

NTBC was utilized for the treatment of HTI in conjunction with a tyrosine restricted diet. It is an inhibitor of 4-hydroxyphenylpyruvate dioxygenase, and thus, this prevents the formation of toxic metabolites such as SA which have been shown to block the of delta 5-aminolevulinic acid dehydratase in the heme biosynthesis. Neurogenic crises in HTI have a physiological basis essentially similar to those occurring in porphyria and lead poisoning in which delta 5-aminolevulinic acid is also increased. The clinical course of neurogenic crises also resembles Guillain-Barré syndrome. Therefore, when HTI patients are admitted with nonspecific symptoms like irritability, pain, weakness, hypertension and
hyponatremia such as our patient, neurogenic crisis should be evaluated as well in order to improve the chance of a correct diagnosis. Before the NTBC era began about 25 years ago, with dietary treatment alone, over 90% of patients died before 12 years of age and 10% of those deaths were caused by neurogenic crises (2). Prior to NTBC, neurogenic crises could emerge at any time and age, particularly crises followed a minor infection. During the NTBC era, severe neurogenic crises may appear when NTBC treatment is interrupted (4-6). In a review of the literature, it can be seen that there are few reports on neurogenic crises in HTI patients following NTBC coming into use. Schlump et al. (5) reported an 8-month-old male who had a severe neurogenic crisis with progressive ascendant polyneuropathy, diaphragm paralysis and arterial hypertension after an interruption of NTBC for 2 months. All neurological signs and symptoms in question disappeared after a resumption of NTBC treatment (5). Neurogenic crises are only currently a problem in some countries owing to a lack of family awareness and health service problems. In 2016, Onenli Mungan et al. (7) reported a nine-month-old boy who had an irreversible neurological crisis after a one-month discontinuation of NTBC and they hypothesized that the duration of NTBC discontinuation is not the only factor determining the reversibility of neurogenic crisis. This again emphasizes the importance of continued patient compliance and that neurogenic crises are only a current problem because of a lack of family adherence to the treatment and health service problems. Our report showed that for HTI patients with nonspecific findings such as vomiting, weakness, hyponatremia and paresthesia or paralysis of the extremities, seizure and arterial hypertension, neurogenic crises should be considered at the outset.

**Ethics**

**Informed Consent:** Informed consent was obtained from the patient’s parents.

**References**


