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Case Report

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

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ABSTRACT

Hereditary tyrosinemia Type I (HTI) 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 hyper 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

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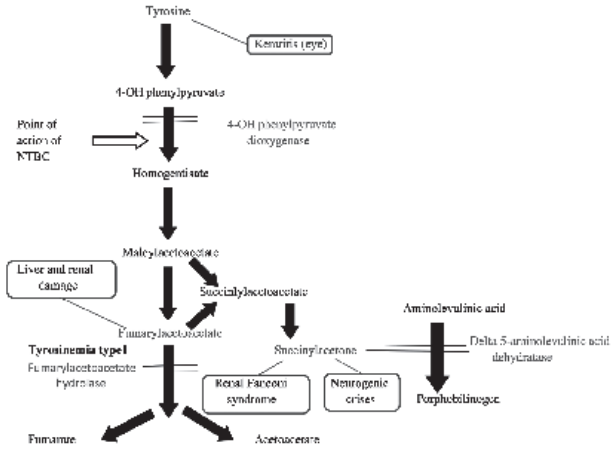

Figure 1. Patway of tyrosine metabolism in tyrosinemia Type I

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¬guineous 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 the age of seven years without any signs of growth, hepatic, renal or neurological deteriorations and never necessitated hospitalization. On physical examination in the emergency service room, he presented weight: 36 kg (90th percentile), height: 134 cm (90th percentile), blood pressure: 148/114 mm hg, compatible with phase 2 hyper tension, fever 37 °C, respiration: 30/min and pulse: 120/min. He looked to be anxious and ill and was in a lateral knee-chest position due to tenderness in the abdomen; nevertheless, defence, rebound, organomegaly and ascites were not observed. Deep tendon reflex examination was normal and there was no parasthesis or pathologic reflex. Laboratory analysis revealed normal glucose, hepatic and renal function tests and acute phase reactants. Abdomen ultrasonography and plain X-ray were performed and no significant findings were determined except for increased bowel gas pattern. Since hyponatremia (Na: 121 mEq/L, N: 136-145) was determined, intravenous saline solution was given. Intravenous glucose was also initiated as an energy source and to block the step before the hydratase (delta-aminolevulinic synthase). Amlodipine treatment was initiated since hypertension was detected with recurrent measurements. At the seventh hour of emergency service follow-up, generalized tonic-clonic seizures were observed followed by hypertonic posture. Antiepileptic treatment was initiated with intravenous dormicum and levetiracetam. We obtained a detailed medical history and learned the truth about the 30-day interruption of NTBC. The patient was evaluated as being in neurogenic crisis and admitted to the pediatric intensive care unit (PICU). At the time of admission to the PICU, furosemide and atenolol treatments were added as the hypertension and Glasgow Coma scale (GCS) of the patient was E3M4V1. At the 24th hour of hospitalization NTBC was reinitiated at a dosage of 2 mg/kg/d. After NTBC was re-administered, neurogenic crisis including seizures, progressive ascending polyneuropathy, hypertonic posture and respiratory distress requiring bilevel positive airway pressure support settled down. Consequently, we did not use haem arginate. Following PICU support of 36 hours, the patient was transferred to the inpatient clinic. At the time of transfer to the inpatient clinic, GCS was E4M6V5 and no seizure was observed during the inpatient clinic follow-up. Antihypertensive treatment was reduced gradually. The patient was discharged from the hospital without any symptoms after six days inpatient clinic follow-up. Amlodipine treatment was gradually reduced and ceased within three weeks, however levetiracetam was used for five months and then ceased. At present, the patient continues the diet and NTBC therapy.

Informed consent was obtained from the patient's parents.

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 these 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.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.Y., E.E., M.A.K., Concept: H.Y., S.K.U., Design: H.Y., E.C., B.K., M.Ç., Data Collection and Processing: H.Y., Analysis and Interpretation: H.Y., Literature Search: E.E., Writing: H.Y.

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