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Effect of nitisinone (NTBC) treatment on the clinical course of hepatorenal tyrosinemia in Québec

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ABSTRACT

Background: Hepatorenal tyrosinemia (HT1, fumarylacetoacetate hydrolase deficiency, MIM 276700) can cause severe hepatic, renal and peripheral nerve damage. In Québec, HT1 is frequent and neonatal HT1 screening is practiced. Nitisinone (NTBC, Orfadin ®) inhibits tyrosine degradation prior to the formation of toxic metabolites like succinylacetone and has been offered to HT1 patients in Québec since 1994.

Methods: We recorded the clinical course of 78 Québec HT1 patients born between 1984 and 2004. There were three groups: those who never received nitisinone (28 patients), those who were first treated after 1 month of age (26 patients) and those treated before 1 month (24 patients). Retrospective chart review was performed for events before 1994, when nitisinone treatment began, and prospective data collection thereafter.

Findings: No hospitalizations for acute complications of HT1 occurred during 5731 months of nitisinone treatment, versus 184 during 1312 months without treatment ($p<0.001$). Liver transplantation was performed in 20 non-nitisinone-treated patients (71%) at a median age of 26 months, versus 7 late-treated patients (26%, $p<0.001$), and no early-treated patient ($p<0.001$). No early-treated patient has developed detectable liver disease after more than 5 years. Ten deaths occurred in non-nitisinone treated patients versus two in treated patients ($p<0.01$). Both of the latter deaths were from complications of transplantation unrelated to HT1. One probable nitisinone-related event occurred, transient corneal crystals with photophobia.

Interpretation: Nitisinone treatment abolishes the acute complications of HT1. Some patients with established liver disease before nitisinone treatment eventually require hepatic transplantation. Patients who receive nitisinone treatment before 1 month had no detectable liver disease after more than 5 years.

1. Introduction

We report the outcome of treatment of hepatorenal tyrosinemia (HT1, MIM 276700) [1], a severe hereditary metabolic disorder of childhood, with nitisinone, which specifically inhibits an early step of tyrosine degradation (Fig. 1) [2]. The setting is the province of Québec, Canada, which is suited for clinical studies of HT1 because the disease is frequent due to high prevalence of a founder mutation, IVS12 + 5G > A [3], in the French-Canadian population [4,5] and because of a universal newborn screening program which refers all

Abbreviations: AFP, alpha-foetoprotein; ALA, delta-aminolevulinic acid; ALT, alanine aminotransferase; FAH, fumarylacetoacetate hydrolase; HT1, hereditary tyrosinemia, type 1; 4HPL, 4-hydroxyphenyllactate; 4HPP, 4-hydroxyphenylpyruvate; PBG, porphobilinogen; SA, succinylacetone; SEM, standard error of the mean.

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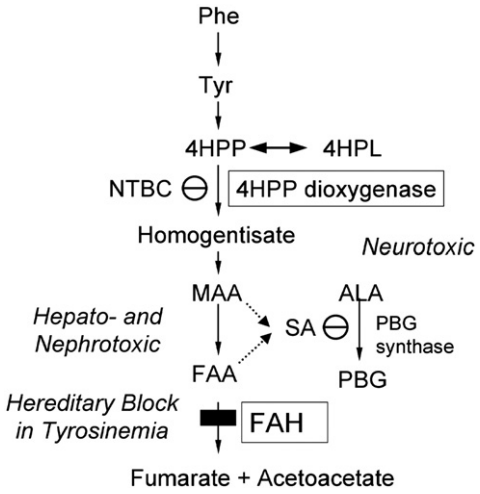

Fig. 1. Nitisinone and tyrosine metabolism. The amino acids phenylalanine (Phe) and tyrosine (Tyr) are degraded as shown. HT1 results from deficiency of the last enzyme, fumarylacetoacetate hydrolase (FAH). Metabolites immediately upstream of FAH, fumarylacetoacetate (FAA) and possibly maleylacetoacetate (MAA), are felt to cause succinylacetone (SA) is a stable derivative of FAA. Elevated levels of SA are pathognomonic for HT1. SA strongly inhibits porphobilinogen synthase, causing secondary accumulation of delta-aminolevulinic acid (ALA) and neurologic crises [8]. Nitisinone (NTBC) potently inhibits 4-hydroxyphenylpyruvic acid (4HPP) dioxygenase and restricts the production of toxic metabolite downstream from this point. Other abbreviation, 4HPL, 4-hydroxyphenyllactic acid.

patients to a small number of physicians, allowing for treatment to be started before the development of clinical symptoms.

HT1 patients typically present in infancy with acute liver failure, cirrhosis, neurologic crises with pain and paralysis [1] and renal tubular dysfunction with hypophosphatemic rickets. Interpatient variability is great. With age, there is increasing risk of hepatocellular carcinoma [6]. Patients who survive beyond infancy may develop chronic renal failure. We compare the outcome of children born during the first ten years that nitisinone was available in Québec with that of patients born in the preceding decade, during which all current treatment options except nitisinone were available, including newborn screening, diet therapy and liver transplantation.

2. Material and methods

2.1. Patient groups

All known HT1 patients in Québec born between February 1984 and February 2004 (Fig. 2) were identified. In all patients, the diagnosis of HT1 was confirmed by the presence of elevated levels of succinylacetone in blood or urine. The clinical course of patients was recorded until hepatic transplantation, death, or August 1, 2009, whichever came first. Data for events before 1994 were obtained from retrospective chart review; subsequent data, by prospective recording. Three patient groups were studied: N, never-nitisinone-treated; L, late treatment (composed of patients who started nitisinone after 30 days of age) and E, early treatment (started on or before 30 days of age). Criteria for inclusion in a nitisinone treatment group included: [1] having received nitisinone for at least 2 weeks and [2] lack of documented noncompliance, defined as admitted refusal of nitisinone, plus having documented, inappropriately low plasma nitisinone levels.

The data of late-treated patients consisted of an initial non-nitisinone-treated period and a later nitisinone-treated period. Each period was analyzed separately when evaluating possibly recurrent HT1-related events.

Since 1994, nitisinone treatment has been offered to and accepted by all nontransplanted HT1 patients in Québec. Three patients who received nitisinone were not included in the nitisinone-treated groups. [1] Patient N28, a non-French-Canadian patient, did not have newborn screening detection. She presented with cirrhosis and hepatocellular carcinoma, and liver transplantation was performed. She is included in the never-NTBC-treated group because she received NTBC for only 1 week. [2] A HT1 patient born outside of Québec was diagnosed at age 5 years by family screening, when typical neurological crises lead to the diagnosis of HT1 in a sibling. He had three neurological crises before receiving nitisinone at the age of 10 years. Later, he repeatedly refused to take nitisinone, had nearly undetectable plasma nitisinone levels and developed neurological crises. [3] This patient, who had a chronic course, was excluded because she was born before 1984.

2.2. Treatment protocol

Participants were enrolled in the ongoing International NTBC Study administered in Gothenburg [6]. Doses of nitisinone were initially fixed at 0.6 or 1.0 mg/kg daily in two daily oral doses. For the first 2 years of the study, patients received a recrystallized preparation of NTBC supplied by S Lindstedt and E Holme. Thereafter, they received commercially-produced nitisinone. After 1999, nitisinone dose was titrated in order to minimize urine SA levels [7]. Dietary restriction of phenylalanine and tyrosine was prescribed, aiming to maintain plasma tyrosine at 200–400 μmol/L.

Pretreatment samples were obtained for assay of plasma tyrosine, phenylalanine and alpha-fetoprotein (AFP) and of urine 4-hydroxyphenylpyruvate (4HPP), 4-hydroxyphenyllactate (4HPL), succinylacetone (SA) and delta-aminolevulinic acid (ALA). Two 12-hour urine collections were performed, starting immediately after the first dose of nitisinone, and 24-hour collections on days 2 and 3. Blood and 24 hour urine samples were obtained on days 7 and 14, at 1, 2, 3, 4 and 6 months, and every 3 months thereafter, for assay of plasma and urinary SA, urinary ALA, plasma amino acids, and plasma nitisinone levels. Collaborating physicians completed physical examination forms and provided results of complete blood count and plasma alpha-foetoprotein (AFP), alanine and aspartate aminotransferases, albumin, protein, gamma-glutamyltransferase, bilirubin, creatinine, urea, electrolytes, blood gases, calcium, phosphate and alkaline phosphatase. Patients were genotyped for the common IVS12 + 5G > A mutation [3]. Abdominal imaging included ultrasound every 6 months and annual computerized tomography or magnetic resonance imaging.

The treatment protocol was approved by the Ethics Committee of CHU Sainte-Justine. Informed consent was obtained before enrollment.

3. Definition of variables and analysis

All hospitalizations related to the acute complications of HT1 were noted, including hospitalizations for preventive treatment and observation during infections. Hospitalizations with neurologic crises, defined as in [8], were noted separately. For descriptive purposes, the total length of hospital stays and the total length of time studied were noted. For comparative statistics, the course of each patient was divided into calendar months. Each month was classified as to whether the patient had received nitisinone during that month, and whether an acute event occurred during the month, i.e., neurological crisis or hospitalization for HT1-related reasons other than a neurological crisis. The dates of liver transplantations and deaths were recorded. The first month of life, during which no HT1-related complication was observed in any patient, was excluded from the calculations. Groups were compared by the Chi square test.