Impaired Cognitive Functioning in Patients with Tyrosinemia Type I Receiving Nitisinone

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Objective To examine cognitive functioning in patients with tyrosinemia type I treated with nitisinone and a protein-restricted diet.

Study design We performed a cross-sectional study to establish cognitive functioning in children with tyrosinemia type I compared with their unaffected siblings. Intelligence was measured using age-appropriate Wechsler Scales. To assess cognitive development over time, we retrieved sequential IQ scores in a single-center subset of patients. We also evaluated whether plasma phenylalanine and tyrosine levels during treatment was correlated with cognitive development.

Results Average total IQ score in 10 patients with tyrosinemia type I receiving nitisinone was significantly lower compared with their unaffected siblings (71 ± 13 vs 91 ± 13; $P = .008$). Both verbal and performance IQ subscores differed (77 ± 14 vs 95 ± 11; $P < .05$ and 70 ± 11 vs 87 ± 15; $P < .05$, respectively). Repeated IQ measurements in a single-center subset of 5 patients revealed a decline in average IQ score over time, from 96 ± 15 to 69 ± 11 ($P < .001$). No significant association was found between IQ score and either plasma tyrosine or phenylalanine concentration.

Conclusion Patients with tyrosinemia type I treated with nitisinone are at risk for impaired cognitive function despite a protein-restricted diet. *(J Pediatr 2014;164:398-401)*.

Hereditary tyrosinemia type I (OMIM 276700) is the most frequent inborn error of tyrosine degradation and results from a defect in fumarylacetoacetate hydrolase (EC 3.7.1.2). Without treatment, the accumulation of toxic metabolites, particularly maleylacetoacetate and fumarylacetoacetate, induces organ dysfunction and carcinogenesis. Patients may present within weeks of birth with gastrointestinal bleeding and liver failure, or later in childhood with failure to thrive, peripheral neuropathy, hepatic cirrhosis, and renal Fanconi syndrome.[1] Hepatocellular carcinoma is a frequent cause of death in early childhood.

Introduction of the drug 2-[2-nitro-4-trifluoromethylbenzoyl]-1, 3-cyclohexanedione (NTBC) in 1992 has dramatically improved the survival of patients with tyrosinemia type I.[2,3] NTBC, now marketed as nitisinone, prevents the accumulation of toxic metabolites by blocking an upstream enzyme, 4-hydroxyphenylpyruvate dioxygenase (EC 1.13.11.27), in the tyrosine degradation pathway.[3] Before the introduction of NTBC, the mortality rate in children diagnosed early (age <2 months) was 75% at age 2 years and >90% by age 12 years.[4,5] Long-term survival was attained only in those who underwent successful orthoptic liver transplantation after the discovery of hepatocellular carcinoma.[6] With the advent of NTBC, liver dysfunction is now controlled in >90% of patients, and extrahepatic manifestations have been abolished.[7] The risk of liver cancer has been reduced as well.[8-10] As a consequence, death in childhood has become a rare event.[11] Concerns whether increased survival is attained at the expense of reduced cognitive functioning remain, however.

Nitisinone biochemically switches the enzymatic defect from tyrosinemia type I to tyrosinemia type III, inducing elevated tyrosine concentrations up to 1500 μmol/L (normal, 40-90 μmol/L) when dietary treatment is not provided.[7] Increased tyrosine levels are considered responsible for the impaired cognitive function in patients with tyrosinemia type II and III.[1] Whether a phenylalanine- and tyrosine-restricted diet aimed at reducing plasma tyrosine concentrations to <500 μmol/L is sufficient to prevent cognitive damage is unknown.

The aim of the present study was to evaluate cognitive functioning in patients with tyrosinemia type I during nitisinone treatment on a protein-restricted diet by comparing their IQ scores with those of their healthy siblings.

Methods

Patients with tyrosinemia type I were retrieved from 2 Dutch centers, University Medical Center Utrecht and University Medical Center Groningen. Patients aged

NTBC 2-[2-nitro-4-trifluoromethylbenzoyl]-1, 3-cyclohexanedione

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>3 years who had ever been treated with nitisinone (at a dose of 0.8-2 mg/kg) and a protein-restricted diet were included. Exclusion criteria were lack of parental consent and failure to perform reliable IQ testing. Unaffected siblings, when available, served as controls. In the event that more siblings were eligible within the same family, the sibling in the same age category as the patient was asked to participate, to allow the use of the same IQ test and to optimize the comparison of the patient and control. A waiver of requirement for informed consent was granted by the Institutional Review Board of the University Medical Center Utrecht, which reviewed the study.

Cognitive functioning was assessed using age-appropriate Wechsler Scale IQ tests (Wechsler Preschool and Primary Scale of Intelligence-Revised for age 3-7 years, Wechsler Intelligence Scale for Children-Third Edition for age 7-17 years, and Wechsler Adult Intelligence Scale-Third Edition for age 18 years and older). These Wechsler tests provide 3 scores: a verbal IQ score, a performance IQ score, and a composite single total IQ score. The mean ± SD score of these tests is 100 ± 15. Assessments took place at the participant's home, in a quiet room, during the daytime by a single investigator. The test results for the patients were compared with the results for the controls as well as with scores of IQ tests performed previously, when available.

Earlier studies have suggested that both tyrosine levels and phenylalanine levels may play a role in cognitive development.[6,9] To monitor the effect of dietary restriction, plasma amino acid concentrations, including phenylalanine and tyrosine, were determined at 3-month intervals during follow-up. These data were retrieved from patient records. Data on clinical manifestations during follow-up, particularly those suggestive of high levels of plasma tyrosine (particularly keratitis), were also collected from hospital records. Parental education, profession, and socioeconomic status were assessed using a questionnaire. The questionnaire also addressed siblings' school performance and health, including the use of medication.

Statistical analyses were performed using SPSS version 14.0 (SPSS, Chicago, Illinois). By defining the skewness (−0.04 ± 0.524), we found a normal distribution of the IQ scores and used the parametric Student *t* test to test for within-group IQ differences between patients and controls. We used the paired Student *t* test to investigate the difference between paired patients and their unaffected siblings. We used Pearson correlation to examine relationships between performance on the IQ test and metabolic parameters in the patients with tyrosinemia type I. A significance level of $P < .05$ was used for all tests.

Results

Sixteen eligible patients with tyrosinemia type I were retrieved. Six patients were excluded, 4 patients because of lack of parental consent and 2 (3 years old) patients because reliable IQ testing could not be accomplished owing to significant developmental delay. Eight of the remaining 10 patients were treated with nitisinone and a protein-restricted diet at the time of testing, whereas 2 had received nitisinone for more than 10 years before undergoing liver transplantation (**Table**). In 7 families, an unaffected sibling served as a control.

Cognitive Measures

The mean total IQ was 71 (range, 58-84) in patients with tyrosinemia type I and 91 (range, 78-104) in their healthy siblings. In patients with tyrosinemia, mean performance IQ was 70 (range, 59-81) and mean verbal IQ was 77 (range, 63-91) compared with 87 (range, 72-102) and 95 (range, 84-106) in their healthy siblings. The IQ difference was seen on both subscales and remained significant when only patients with an available sibling were analyzed (71 vs 91; $P = .006$). The 2 patients who were no longer treated with nitisinone and a protein-restricted diet after undergoing liver transplantation had similarly low IQ levels. Low IQ scores were associated with special education attendance ($r = -0.0677$; $P = .036$).

In search of an explanation for these findings, we next focused on a subset of 5 patients from a single center. In this center, IQ tests were repeated at 2- to 3-year intervals as a regular part of follow-up. We reasoned that a stable IQ over time would point toward preexisting factors, whereas a decline in IQ would suggest ongoing damage during—and perhaps due to—treatment. As depicted in **Figure 1**, initial IQs were within the normal range in 4 of the 5

Table. Baseline characteristics of patients with tyrosinemia type I

Patient	Age at time of study, y	Sex	Age at diagnosis, mo	Age at start of nitisinone use, mo	Current NTBC use	Liver transplantation	History of keratitis	Unaffected sibling included	Education	SES
1*	20	Male	3	78	Yes	No	Yes	Yes	Regular	Low
2	20	Female	9	72	No†	Yes	No	Yes	Regular	Low
3	16	Male	6	6	Yes	No	Yes	Yes	Regular	Middle
4	14	Male	8	8	Yes	No	Yes	Yes	Regular	Middle
5	13	Male	3	3	Yes	No	Yes	Yes	Special	Low
6	13	Male	24	24	No‡	Yes	No	No	Special	Middle
7*	11	Male	0	0	Yes	No	Yes	Yes	Regular	Low
8	10	Male	6	6	Yes	No	Yes	Yes	Special	Low
9	9	Male	4	4	Yes	No	No	Yes	Regular	High
10	5	Female	3	3	Yes	No	No	No	Regular	Middle

SES, socioeconomic status.
*Patients 1 and 7 are siblings.
†At age 18 y.
‡At age 8 y.