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Long-term cognitive functioning in individuals with tyrosinemia type 1 treated with nitisinone and protein-restricted diet

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ABSTRACT

Introduction: Tyrosinemia Type 1 (HT1) is an autosomal recessive disorder caused by a defect in the enzyme fumarylacetoacetate hydroxylase in the tyrosine pathway. Implementation of nitisinone (NTBC) treatment has dramatically improved survival rate of individuals with HT1, yet recent reports on cognitive impairment in treated patients exist.
Aims: Describe long-term neurocognitive outcome individuals with HT1 treated with nitisinone and protein restricted diet.
Methodology: Twelve individuals with HT1 were analyzed with respect to psychomotor development and cognitive functioning using standardized psychometric tests. Plasma tyrosine and phenylalanine concentrations were also collected and analyzed, as part of the regular HT1 follow up program in our clinic.
Results: Delayed performance in Bayley scale mental developmental index (MDI) was identified in 29% to 38% of the patients assessed at different ages. At preschool age, mean full scale IQ (FSIQ) was 88 ± 16; six out of nine assessed children preformed within normal range, and one child presented with intellectual disability. At school age mean FSIQ was 79 ± 18, three out of nine children preformed within normal range and two showed intellectual disability. Repeated measures showed IQ decline over time in four out of eight patients, all of whom presented with symptoms in their first months of life. Patients that showed no progressive IQ decline were 8 months or older at diagnosis, with a mean age of 17 months. Significant correlation between Phe/Tyr ratio and FSIQ at school age was identified ($r = -0.689$; $p < 0.044$).
Conclusion: Some patients with HT1 treated with nitisinone and protein restricted diet are at risk of presenting developmental delay and impaired cognitive functioning. Patients with early onset of symptoms could be at risk for progressive cognitive functioning decline over time.

1. Introduction

Tyrosinemia Type 1 (HT1) is an autosomal recessive disorder caused by a defect in the fumarylacetoacetate hydroxylase enzyme catalyzing the last step of tyrosine breakdown. Toxic metabolites are formed including succinylacetone, maleylacetoacetate and fumarylacetoacetate that are responsible for the hepatic and renal manifestations of the disease. In 1992, the compound 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC, nitisinone) began to be used in the treatment of HT1, to prevent the accumulation of toxic metabolites. Implementation of nitisinone treatment has dramatically improved survival rate of individuals with HT1 [8].

Survival improvement is directly correlated to age at treatment initiation, especially when nitisinone is introduced during the first weeks of life [20] and hepatocellular carcinoma has not developed in the 5 first years of follow up. These findings explain the incorporation of HT1 to national newborn screening programs in several countries. With survival improvement, long-term complications such as cognitive impairment have been described.

Cognitive functioning in patients with HT1 has recently been studied with very diverse results. Masurel-Paulet et al. [9] first reported a high frequency of cognitive impairment causing schooling problems in a retrospective study of 46 patients with HT1 treated with nitisinone. In this sample, 35% of 23 school age children had schooling difficulties and 6 children had major cognitive disturbances. However, this retrospective study lacked specific psychometric testing.

Several single-center studies assessing intelligence quotient (IQ) in small groups reported an average IQ in HT1 patients below the normal range, but with important intragroup variability. None of these studies

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were able to identify a clear correlation between metabolic control and cognitive functioning [2,4,5]. A high frequency of variable dysfunction or retardation in language development was identified in one study [14].

Different results were reported by Pohorecka et al. [11] in a group of 9 Polish children with HT1. Children were assessed with WISC R and all performed within the normal range on all scales. In this group no emotional or behavioral problems were identified. Only attention difficulties were reported, which the authors considered might be associated with plasma tyrosine levels.

Patients with HT1 might be at risk of progressive cognitive deterioration over time. Bendadi et al. [4] reported results on 5 patients in which IQ tests were repeated at 2- to 3-year intervals. An average drop of 27 IQ points was observed. Also poorer executive functioning (working memory and cognitive flexibility) and social cognition compared to healthy controls has been reported [15].

The present study reports results on the long-term cognitive functioning in individuals with HT1 treated with nitisinone and protein restricted diet.

This is one of the longest and largest reports on neurocognitive functioning in patients with HT1 under NTBC treatment. Being a single-center study, all patients were treated and assessed using the same protocol.

2. Material and methods

2.1. Subjects

The present is a retrospective, single center study. At INTA, 17 patients have been diagnosed and treated for HT1. Of the total group, one patient died due to hepatocellular carcinoma before a liver transplant could be performed and another died from complications after liver transplant. Two successful liver transplants have been performed; one patient who successfully received a liver transplant was excluded because she did not receive nitisinone and was lost to follow-up. Informed consent was not obtained for one of the patients and one patient who was recently diagnosed was not included because psychometric evaluation had not yet been performed. Previously most of the HT1 patients were included in an international multicenter research project on nitisinone [21].

Data collected between 1996 and 2015 on twelve individuals with HT1 treated with nitisinone and a protein-restricted diet were analyzed in the present study (Table 1). All had been clinically diagnosed, with a confirmed diagnosis at a mean of 9.8 months of age. Nitisinone treatment was initiated between 2 and 42 months of age, with a mean of 27 months. One of the patients required a liver transplant, but this patient's cognitive functioning data are from prior to the transplant.

Treatment was initiated immediately after diagnosis in all patients. Nitisinone was administered at a 1 mg/kg/day bodyweight dose. The targeted NTBC serum concentration was between 30 and 60 μmol/L [6]. NTBC dose was adjusted according bodyweight, and seeking to maintain succinylacetone in plasma complete suppression.

All children were prescribed a low-phenylalanine (PHE), low-tyrosine (TYR) diet designed to meet their needs for growth without providing excesses of these amino acids, according to RDI [6] Supplementation with mixture of amino acids free of TYR and PHE was prescribed for all patients. All though during some periods, children did not follow the indication, due to the high cost of the formula. None of the patients received phenylalanine supplementation due to phenylalanine concentrations below the lower target limit (<35 μmol/L).

2.2. Instruments

Psychomotor development was assessed with Bayley-II during infancy, and cognitive performance at preschool and school age with Wechsler age appropriate scales. Mean plasma tyrosine and phenylalanine levels during first three years of life and the complete treatment period were analyzed. All patients had their routine blood analysis done every three months, in the same dates.

– The Bayley [3] scales of Infant Development Second Edition assesses psychomotor development from the first month of life until 42 months of age. Standard scores are derived for a mental development index (MDI) and a motor or performance development index

Table 1
Characteristics of the individuals.

Patient	Age at time of study	Sex	Age at diagnosis (months)	Age at start of NTBC	Education	NTBC serum μmol/L	Mean Tyr[a] μmol/L	Mean Phe[a] μmol/L	Relevant information	Psychomotor and cognitive functioning	Symptoms at diagnosis
1	19 y, 7 m	Female	2 m	3 m	Regular	39 ± 20	587 ± 220	75 ± 21		Borderline IQ	Acute hepatic failure
2	17 y, 4 m	Female	36 m	42 m	Regular	48 ± 19	656 ± 71	80 ± 20		Borderline IQ	Rickets-hepatosplenomegaly
3	14 y, 2 m	Male	2 m	4 m	Special	38 ± 10	267 ± 128	65 ± 28	History of child neglect	Intellectual disability	Hepatosplenomegaly-nephrocalcinosis rickets
4	12 y, 5 m	Male	11 m	11 m	Regular	38 ± 11	381 ± 163	80 ± 31		Normal IQ	Rickets-hepatosplenomegaly
5	12 y, 5 m	Male	9 m	10 m	Regular	42 ± 18	428 ± 247	67 ± 28		Normal IQ	Acute hepatic failure
6	12 y, 7 m	Female	8 m	9 m	Regular	38 ± 12	533 ± 245	85 ± 32		Normal IQ	Acute hepatic failure, Rickets
7	10 y, 9 m	Female	3 m	4 m	Regular	37 ± 13	583 ± 303	93 ± 26		Borderline IQ	Acute hepatic failure, Coagulopathy
8	9 y, 9 m	Male	1 m	1 m	Regular	30 ± 8	444 ± 155	88 ± 26	ADD	Intellectual disability	Acute hepatic failure
9	7 y, 6 m	Female	6 m	8 m	Regular	41 ± 14	381 ± 159	107 ± 14	Epilepsy, Ulcerative colitis	Borderline IQ	Hepatomegaly
10	5 y, 5 m	Female	4 m	6 m	Regular	22,6 ± 5	236 ± 122	95 ± 56	Pre-term birth	Normal IQ	Hepatosplenomegaly - Acute hepatic failure
11	3 y, 8 m	Male	11 m	12 m		40 ± 14 [b]	187 ± 100 [b]	93 ± 31 [b]		Normal motor and mental development	Rickets hepatosplenomegaly
12	1 y, 8 m	Male	10 m	10 m					Neonatal asphyxia	Developmental delay	Acute hepatic failure, Hepatosplenomegaly, hypoglycemia

[a] From diagnose to moment to last assessment.
[b] Data not included due to limited number of samples due to age.