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Girl With Tyrosinemia Type 1 and Executive Dysfunctions Treated With Methylphenidate: A Case Report

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Abstract

Hereditary tyrosinemia type 1 (HT1; OMIM 27670) is an inborn error of tyrosine metabolism, caused by a deficiency of the enzyme fumarylacetoacetate hydrolase. This defect leads to accumulation of toxic products, which cause liver and kidney dysfunction. In patients with HT1, IQ, executive functioning, and social cognition are also affected. We report here a case report of a Belgian 11-year-old girl of Moroccan ethnicity with HT1. She had attention problems, which had a significant impact on her school functioning. Neuropsychological tests showed very low scores for processing speed and executive functioning. Therapies such as adaptations in the school and private tutoring were not sufficient to improve this. Treatment with methylphenidate showed a significant improvement in the neuropsychological test and school functioning. This case shows the importance of being alert for problems with executive functions in patients with HT1 and to consider psychopharmacological treatment.

Keywords

tyrosinemia, executive functioning, methylphenidate, school achievement, NTBC

Introduction

Hereditary tyrosinemia type 1 (HT1) is an inborn error of tyrosine metabolism, caused by a deficiency of the enzyme fumarylacetoacetate hydrolase. This defect leads to accumulation of toxic products which cause liver and kidney dysfunction.[1] Before the treatment with 2-(2-nitro-4-trifluoromethylbenyol)-1,3-cyclohexanedione (NTBC), which prevents the accumulation of toxic metabolites by inhibiting the tyrosine catabolism upstream from the primary enzymatic defect, patients have severe liver dysfunction, renal tubulopathy, cardiomyopathy, porphyria-like syndrome, and hepatocellular carcinoma and often need a liver transplantation.[2] Nevertheless, patients under NTBC and dietary treatment shown to have lower IQ, school problems, impaired motor control, and problems with executive functioning and social cognition.[3]

Case Report

The girl described in this case report was the firstborn of consanguineous Moroccan parents. She was born after an uneventful pregnancy and partus. During the first year of life, her mother consulted several physicians due to persistent vomiting, failure to thrive, and swollen abdomen. Diagnosis of HT1 came at the age of 11 months. She was referred to the metabolic specialist because of dystrophia, distended abdomen, and elevated serum transaminases. Clinical examination showed hepatomegaly, but no splenomegaly, hypotonia, and psychomotor retardation. Laboratory investigations revealed extreme tyrosyluria succinylacetone in the organic acids in urine. Amino acids

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showed an increase in L-tyrosine, suggesting tyrosinosis. The diagnosis of HT1 was confirmed by enzyme assay in leukocytes showing a very low activity of fumarylacetoacetase. Treatment with NTBC (2 mg/kg body weight/day) and dietary treatment (0.5 g/kg body weight natural proteins supplemented with the amino acids mixture TYR 1 [Milupa, Germany] 1.0 to 1.2 g/kg body weight/day) were started and gave a good clinical and biochemical improvement: disappearance of succinylation in urine, mean plasma L-tyrosine level of 260 μmol/L (Reference: 200 μmol/L-400 μmol/L), and L-phenylalanine level of 64 μmol/L (Reference: 26 μmol/L-98 μmol/L). However, based on the elevation of serum alkaline phosphatase and α-fetoprotein and the risk of developing hepatocarcinoma, a liver transplantation was performed.

After the start of therapy, her growth and weight improved. The girl's development was slightly retarded for motor skills and language. She started school at the age of 2.5. She had a liver transplantation at the age of 3.

Her progress was below average, but nevertheless she started primary school at the age of 6. She had extra support but had to repeat the first grade because of problems with learning and absence because of frequent illness. Until the fifth grade, she had extra tutoring for mathematics. School results were still poor, and school suggested to stop primary school without receiving her degree and go to a preparatory year of secondary school. At this time, we examined the girl for cognitive functioning (intelligence and neuropsychological investigation).

Psychological tests showed a borderline (well below average) intelligence. There were low average scores for fluid intelligence (Gf), crystallized intelligence (Gc), and visual processing (Gv) and low to average scores for working and short-term memory (Gsm). However, there were extremely low scores for processing speed (Gs) and executive functioning. Moreover, these scores were significantly lower opposed to the other broad abilities. There were also problems with selective attention and attention fluctuations. There was an impact on the school functioning and it was uncertain whether the girl would receive her certificate of primary school. During primary school, problems with attention and distraction were reported. She also got extra support through private tutoring and speech therapy. Based on these tests and the problems at school, psychopharmacological treatment (methylphenidate) was started and evaluated after electrocardiogram (ECG) and agreement from the liver transplant team and metabolic specialist. We started with methylphenidate 2 × 5 mg/d, which was elevated to 2 × 10 mg/d. A new investigation was performed 3 weeks after start-up. The retest battery included tasks that measure processing speed (Gs), working and short-term memory (Gsm), selective attention, and executive functioning.

Evaluation by neuropsychological testing under treatment with methylphenidate showed a massive improvement, also as the results at the school, which continued over the last year in primary school. The advice from school changed and she started regular secondary school, where she is still performing well.

Table 1. Processing Speed Test Results Measured by the WISC-III-NL Factor VS and the Bourdon-Vos Speed Standard Score.[a]

Test	Before Treatment	After Treatment
WISC-III-NL factor VS	65	91
Bourdon-Vos standard score speed	79	102

[a]Results are shown in standard scores, average 100, standard deviation 15. Test results show an improvement in processing speed after treatment.

Table 2. Selective Attention Test Results Measured by the Bourdon-Vos Test.[a]

Executive Function	Before Treatment	After Treatment
Speed (RT tot)	17.6	13.1
Accuracy (TNE)	11	4
Attention fluctuations (sd RT)	2.63	1.44

Abbreviations: RT tot, average row time, normal range 14.7 ≥ RT ≥ 11.9; Sd RT, standard deviation row time, normal range 1.9 ≥ Sd ≥ 1.3; TNE, total number of errors.

[a]Test results show an improvement in speed, accuracy, and less attention fluctuations after treatment.

Methods

A standard intelligence test was performed using the WISC-III-NL[4] and the SON-R 6-40[5] to get insight on the different broad abilities of intelligence, including processing speed, which was suspected to be impaired based on school results and daily functioning, and working memory. The Bourdon-Vos Test[6] was used as a measurement for selective attention, more specifically to get insight on processing speed and accuracy during a sustained attention task. Attention fluctuations were also measured. Finally, 3 different aspects of executive functioning were measured using the Delis-Kaplan executive function system.[7] For response inhibition, the D-KEFS[7] Color-Word Interference Test was performed. For cognitive flexibility, the D-KEFS[7] Trail Making Test was used, and for planning and organization, the D-KEFS[7] Tower Test was used.

Results

Results show higher scores for processing speed (Gs) under treatment with methylphenidate, measured by the WISC-III-NL factor score VS and the Bourdon-Vos standard score for speed (Table 1). Additionally, the Bourdon-Vos test measured a faster speed, lower amount of mistakes, and no more attention fluctuations under treatment (Table 2). These findings indicate a faster processing speed and better selective attention under treatment with methylphenidate in this patient.

Concerning executive functioning, higher scaled scores were found on the inhibition task and the inhibition/switching task of the D-KEFS Color-Word Interference Test after treatment. Additionally, there were less mistakes made on the inhibition/switching task under treatment (Table 3). These findings

Table 3. Executive Functioning—Response Inhibition Test Results Measured by the D-KEFS Color-Word Interference Test.[a]

Test and Subtest	Before Treatment	After Treatment
D-KEFS Color-Word Interference Test		
Color naming	5	7
Word reading	8	9
Inhibition	1	6
Inhibition/switching	1	9
Inhibition total errors	9	8
Inhibition/switching total errors	9	12
D-KEFS Trail Making Test		
Visual scanning	7	10
Number sequencing	10	12
Letter sequencing	8	9
Number–letter switching	8	10
Motor speed	7	9
Number–letter switching total errors	12	12
D-KEFS Tower Test		
Total achievement score	5	11
Average time of first step	10	12
Time per step rate	8	11
Step accuracy rate	7	10
Rule errors	10	10

[a] Cognitive flexibility test results measured by the D-KEFS Trail Making Test. Planning test results measured by the D-KEFS Tower Test. Results are shown in scaled scores, average 10, deviation 3. Test results show an improvement in response inhibition, cognitive flexibility, and planning skills after treatment.

show improved abilities in inhibitory control under treatment in this patient. There was also a higher scaled score found on number/letter switching task of the D-KEFS Trail Making Test under treatment (Table 3). This shows a better cognitive flexibility under treatment. Finally, higher scaled scores were found on all abilities of the D-KEFS Tower Test (Table 3), which proves a better planning and organization under treatment.

There was no difference found in scaled scores for both subtests of the WISC-III-NL that measure working and short-term memory, Digit Span and Arithmetic, under treatment (Table 4). This shows no improvement in working and short-term memory (Gsm).

Discussion

This case report of a child with HT1 and executive problems, who had a significant improvement in her processing speed and executive functioning, shows the importance of thorough neuropsychological investigations in these types of patients. After the diagnosis of the neuropsychological problems in this child, and proper treatment, including treatment with methylphenidate, her possibilities on school choice changed dramatically because of her better achievements under treatment with methylphenidate. Where she was first advised to stop primary school before ending it with a degree and being referred to a preparatory year of secondary school, which has less career opportunities, now she was able to finish primary school in the standard way and she is doing well in regular secondary school.

Table 4. Working Memory Test Results Measured by the WISC-III-NL Subtests Digit Span and Arithmetic.[a]

Subtest	Before Treatment	After Treatment
Digit span	9	8
Arithmetic	2	2

[a] Results are shown in scaled scores, average 10, deviation 3. Test results show no improvement in working memory after treatment.

Declaration of Conflicting Interests

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