



Psychological Assessment of Patients With Biotin-Thiamine-Responsive Basal Ganglia Disease

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Abstract

Biotin-thiamine-responsive basal ganglia disease is a devastating autosomal recessive inherited neurological disorder. We conducted a retrospective chart review of all patients with biotin-thiamine-responsive basal ganglia disease who underwent a formal psychological assessment. Six females and 3 males were included. Five patients (56%) had an average IQ, two patients (22%) had mild delay, and two (22%) had severe delay. A normal outcome was directly related to the time of diagnosis and initiation of treatment. Early diagnosis and immediate commencement of treatment were associated with a favorable outcome and vice versa. The most affected domain was visual motor integration, while understanding and mathematical problem-solving were the least affected. In summary, this is the first study discussing the psychological assessment of patients with biotin-thiamine-responsive basal ganglia disease. The results of this study alert clinicians to consider prompt initiation of biotin and thiamine in any patient presenting with neuroregression and a basal ganglia lesion on a brain magnetic resonance imaging.

Keywords

biotin-thiamine-responsive basal ganglia disease, biotin-responsive basal ganglia disease, thiamine, biotin, psychological assessment

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Background

Biotin-thiamine-responsive basal ganglia disease, or thiamine metabolism dysfunction syndrome 2 (MIM: 607483), is an autosomal recessive inherited neurometabolic disorder. It was first described in 1998 by Ozand et al as biotin-responsive basal ganglia disease and then renamed in 2013 by Alfadhel et al as biotin-thiamine-responsive basal ganglia disease.^{1,2} It is characterized by neuroregression with subacute encephalopathy, confusion, dysarthria, and ophthalmoplegia, and it progresses to severe cogwheel rigidity, dystonia, quadriparesis, and finally death if left untreated. Radiologically, the patients presented with high T2 signal intensity in the basal ganglia (caudate and putamen) with diffuse cortical and subcortical white matter and infratentorial brain lesions in acute crises, while in chronic follow-up, they have atrophy and necrosis of the basal ganglia. The disease is linked to 2q36.3 and found to be caused by a mutation in the *SLC19A3* gene, which encodes the second thiamine transporter.^{1,3} Interestingly, there are no biochemical abnormalities reported in this neurometabolic disorder.^{1,3-5} Measurement of the free thiamine level in cerebrospinal fluid (CSF) and fibroblasts could be a useful biomarker for

diagnosis and treatment monitoring.⁶ The diagnosis is achieved via sequencing of the *SLC19A3* gene defect. Remarkably, this form of *SLC19A3* gene defects is responsive to biotin and thiamine, and immediate commencement of treatment with biotin and thiamine is usually associated with a better outcome.¹ Although this disease was first described long ago, there are not enough follow-up reports with regard to formal psychological assessments for these patients. Psychological assessment in counseling and clinical practice is a means of

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measuring a person's mental, emotional, or intellectual capacity for performing or completing a task. It is an essential parameter for evaluating the long-term outcome of chronic disease. In this study, we report the formal psychological assessments for nine patients diagnosed at King Abdulaziz Medical City, Riyadh, Saudi Arabia, which helps in understanding the natural history of such disease. To the best of our knowledge, this is the first report in the literature discussing such an important element of this treatable neurometabolic condition.

Method

Patient Data

A retrospective chart review was conducted for all patients with biotin-thiamine-responsive basal ganglia disease attending the biochemical genetics (metabolic) and psychology clinics, who underwent formal psychological assessments at King Abdulaziz Medical City in Riyadh, Saudi Arabia, between 2014 and 2017. The diagnosis of biotin-thiamine-responsive basal ganglia disease was confirmed in all participants by DNA molecular testing of the *SLC19A3* gene.

Test Description

The psychological assessment was conducted by a licensed neuropsychologist, and the tests used were as follows: Raven Progressive Matrices, test for reception of grammar, the Developmental Test of Visual–Motor Integration, the Vineland Adaptive Behavior Scale (Interview Edition), and an IQ assessment. For details of the tests, see supplemental material.

Result

Table 1 summarizes the demographic and psychological assessment findings for the cohort. In total, 9 patients were included. There were 6 females and 3 males. All patients were of Saudi origin. All patients had the same homozygous missense mutation in exon 5 of the *SLC19A3* gene [c.1264 A>G (p. T422A)]. The ages ranged between 18 months and 23 years. The age of onset ranged between 4 months and 4 years, and the age of diagnosis ranged between 6 months and 4 years. 5 patients (56%) had an average IQ, 2 (22%) had mild delay, and 2 (22%) had severe delay. Regarding adaptive behavior, 2 (22%) patients were in the adequate range, 2 (22%) were in the mild deficit range, 3 (34%) were in the moderate deficit range, and 2 (22%) were in the profound deficit range of adaptive behavior. Poor visual motor integration was elucidated in 5 (55%) patients. The test for reception of grammar results were average in 5 (84%) of the 6 patients tested, while 1 (16%) patient had poor recognition of grammar. There was a clear correlation between the IQ test results and the test for reception of grammar results, such that all patients with average IQ results had average recognition of grammar. On the other hand, the IQ results were not concomitant with the Vineland Adaptive Behavior Scale results; 3 out of 5 patients who had average IQ scores had a moderate deficit in the Vineland Adaptive

Behavior Scale. Two patients had average scores on both tests, and 1 patient had borderline IQ and a moderate deficit in the Vineland Adaptive Behavior Scale.

Discussion

This is the first report in the literature that discusses the formal psychological assessment of such a devastating neuropsychiatric disease. Interestingly, the long-term outcome is directly correlated with the delay in diagnosis and the initiation of treatment with biotin and thiamine. Immediate diagnosis and initiation of treatment resulted in normal IQ in 100% of cases, while delayed diagnosis and treatment resulted in poor outcomes. Interestingly, it was clear that the patients with biotin-thiamine-responsive basal ganglia disease had no difficulties with understanding and solving mathematical problems, while the most affected domain was visual motor integration, which was affected even in cases with average intelligence.

The prognosis of biotin-thiamine-responsive basal ganglia disease is multifactorial. It depends mainly on the following factors: age of onset, time of diagnosis, time of treatment initiation, and type of mutations. Early age of onset is associated with poor outcomes. Early diagnosis and initiation of treatment is associated with favorable outcomes.^{1,5,7–10} Missense mutations are associated with a good response to biotin and thiamine, while nonsense and frameshift mutations seem to be unresponsive. This difference could be explained by the theory that the vitamin treatment should be effective if the transport capacity reduces the physiological levels that occur in the case of missense mutations, while it seems unlikely to be beneficial in cases where the transporter function is completely abolished, such as cases with nonsense and frameshift mutations.¹¹

The treatment comprises a combination of biotin and thiamine for life. Acute crises will occur if the treatment is discontinued, and this will be associated with poor outcome.¹ Of note, Tabarki et al conducted a randomized controlled trial and concluded that there was no difference in the long-term outcome between 2 groups treated with thiamine alone or with a combination of biotin and thiamine.¹²

The main limitations of the study include selection and information bias due to the limited number of patients and the retrospective nature of the study. Unfortunately, we did not have a baseline psychological assessment of the patients to use for comparison. Additionally, the psychological assessment is limited in young patients. Finally, long-term follow-up psychological assessment is needed for these patients to assess the response to treatment. A larger cohort might be needed for more accurate results in future studies.

Conclusion

This the first reported study regarding a formal psychological assessment of patients with biotin-thiamine-responsive basal ganglia disease; this study confirms that the long-term outcome is directly correlated with the time of diagnosis and initiation of treatment with biotin and thiamine. We alert clinicians to

Table 1. Psychological Assessment of Patients.

Patient Number	Gender	Age of Onset	Age at Diagnosis and Treatment Initiation	Age at the Psychological Assessment	Scales/Tests	Summary (Age Level)
1	F	4 m	9 m	1 y and 6 m	• VABS	• Mild deficit adaptive behaviors (1 y)
2	M	6 y	6 y	10 y and 4 m	• Complete set ^a	• Average IQ; Full IQ = 94 ± 5 , • average recognition of grammar (8 y), • poor visual motor integration (5 y and 10 m), • adequate adaptive behaviors (9 y and 7 m)
3	M	2 y	2 y	22 y and 9 m	• Complete set ^a	• Average IQ; full IQ = 95 ± 5 , • above average recognition of grammar (>11 y), • acceptable visual motor integration (14 y and 6 m), • moderately low adaptive behaviors (15 y and 2 m)
4	M	14 m	17 m	14 y and 9 m	• Complete set ^a	• Borderline IQ; full IQ = 77 ± 5 , • poor recognition of grammar (5 y and 9 m), • poor visual motor integration (5 y and 1 m), • moderate deficit adaptive behaviors (6 y and 3 m)
5	F	2 y	5 y	9 y and 7 m	• VABS	• Severe deficit adaptive behaviors (9 m)
6	F	6 m	6 m	4 y and 4 m	• Complete set ^a	• Average IQ; full IQ = 98 ± 5 , • average recognition of grammar (4 y and 3 m), • low average visual motor integration (3 y and 6 m), • moderately low adaptive behaviors (3 y and 2 m)
7	F	3 y and 6 m	3 y and 6 m	10 y and 5 m	• Complete set ^a	• Average IQ; full IQ = 100 ± 5 , • average recognition of grammar (10 y), • poor visual motor integration (6 y and 10 m), • mild deficit adaptive behaviors (7 y and 9 m)
8	F	5 m	17 m	11 y and 6 m	• VABS	• Profound deficit adaptive behaviors (1 y & 1 m)
9	F	4 y	4 y	4 y and 11 m	• Raven's Matrices • TROG • VABS	• Average IQ; 25th percentile, • average recognition of grammar (4 y and 3 m), • adequate adaptive behaviors (4 y and 6 m)

Abbreviations: m, months; SB-5, Stanford–Binet Intelligence Scale–Fifth Edition; TROG, test for reception of grammar; VABS, Vineland Adaptive Behavior Scale; VMI, Developmental Test of Visual–Motor Integration, y, years.

^aComplete set: Raven's Matrices, SB-5, TROG, VMI, VABS.

consider the commencement of biotin and thiamine in any patient presenting with neuroregression and basal ganglia involvement on brain magnetic resonance imaging.

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Author Contributions

MAF performed the majority of the work associated with preparing, writing, and submitting the manuscript and contributed to the clinical

diagnosis and management of the patients. AAB performed the psychological assessments of the patients.

Declaration of Conflicting Interests

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Ethical Approval

This study was approved by the institutional review board office at King Abdullah International Medical Research Centre (KIMARC; study number: RC16/113/R). Written consent was obtained from each participating patient or their parents.

Supplemental Material

Supplemental material for this article is available online.

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