

Biotin-Thiamine-Responsive Basal Ganglia Disease: Case Report and Follow-Up of a Patient With Poor Compliance

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Abstract

Background: Biotin-thiamine-responsive basal ganglia disease (BTBGD) is a rare treatable autosomal recessive neurometabolic disorder characterized by progressive encephalopathy that eventually leads to severe disability and death if not treated with biotin and thiamine supplements. **Objectives:** We aimed to determine the optimal management of BTBGD presenting in acute encephalopathic episodes. **Method:** Case report. **Results:** An 8-year-old girl born to consanguineous parents was diagnosed with BTBGD at the age of 3 years after presenting with acute encephalopathy and ataxia. The patient was treated with biotin and thiamine, and the family was instructed to continue these medications for life. When she was 7 years old, her supplements were stopped for 2 weeks for social reasons. Afterward, the patient began to have tremor in both hands and an unsteady gait. The family then resumed the medications at the usual dosages. However, the patient remained symptomatic. The patient was admitted with acute BTBGD because of discontinuation of medications. The patient's condition was then managed with high doses of intravenous thiamine and oral biotin. She showed gradual improvement after 48 hours. She was then discharged home 1 week later with residual mild upper and lower limb tremor, as well as right lower limb dystonia. Further follow-up showed a good neurological condition with no apparent long-term sequel. The family was further educated about the importance of strict compliance. **Conclusion:** Patients with BTBGD should remain on lifelong treatment with thiamine and biotin. For those who present with acute relapse, we recommend inpatient treatment with high doses of intravenous thiamine and oral biotin. Further clinical research is required to determine the optimal doses and durations.

Keywords

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

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Biotin-thiamine-responsive basal ganglia disease (BTBGD; MIM: 607483), also known as thiamine metabolism dysfunction syndrome 2 (or thiamine-responsive encephalopathy type 2), is a rare treatable autosomal recessive neurometabolic disorder characterized by progressive encephalopathy. Ozand et al^{1,2} first described it in the literature in 1998 after 10 patients were diagnosed with the disease.

Since then, additional cases have been reported, and in 2005, the mutation was mapped to the human SLC19A3 gene in chromosome 2q37.³ The encephalopathy is of early onset (usually before the age of 4 years), and in most reported cases, the manifestations were preceded by febrile illness that eventually led to severe disability, ataxia, dystonia, seizures, and death if the patients were not treated with biotin and thiamine supplements.¹

As published in previous studies, the doses required to maintain a good neurological outcome and to decrease the risk of crisis are 5 to 10 mg/kg/d for biotin and 40 mg/kg/d for thiamine which should be started once the diagnosis is suspected and

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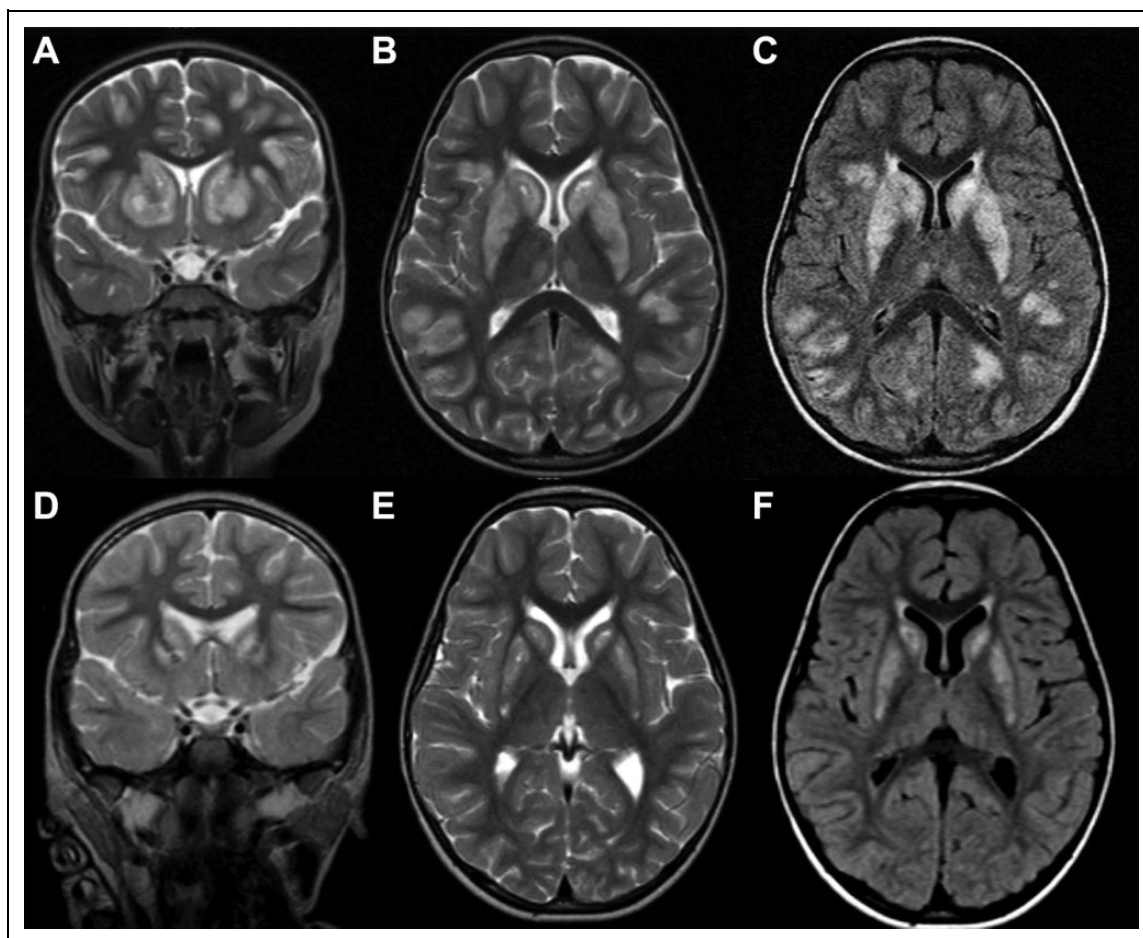


Figure 1. Magnetic resonance imaging (MRI) of the brain with T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences showing high signal intensity in the basal ganglia bilaterally at the time of the initial presentation at the age of 3 years (A, B, C). Significant improvement 1 month later (D, E, F).

continue for life.^{1,4,5} The overall neurological and psychological outcome is related to the time of diagnosis and the initiation of treatment.⁵

Case Report

An 8-year-old girl presented at the age of 3 years with progressive ataxia and excessive salivation, followed by irritability, excessive crying, and a decrease in her oral intake for 3 days. No history of seizure or a decreased level of consciousness was present. No history of fever, either. She had a history of upper respiratory tract infection that was managed with an antibiotic 3 weeks prior to the appearance of her symptoms. She is born to consanguineous parents (first cousins from the paternal side) with no family history of inherited disorders. She had an older sister who developed ataxia at the age of 1 year and died at the age of 18 months with progressive neuroregression and was suspected to have mitochondrial disease. Further information about her sister's illness was not available. In addition, she has a brother, 1 year old, who is normal.

A physical examination showed her to be extremely irritable, with inconsolable crying. A full neurological

assessment revealed a normal cranial nerve with normal power and deep tendon reflexes, along with a positive Babinski reflex. The initial impression was acute disseminated encephalomyelitis (ADEM) to rule out meningoencephalitis or mitochondrial disease.

Initial laboratory test results revealed a normal complete blood count and cerebrospinal fluid analysis with normal glucose, protein, and lactic acid. A brain computed tomography scan showed multiple hypodense areas, and brain magnetic resonance imaging (MRI) showed multiple areas of abnormal signal intensity, which was high on the fluid-attenuated inversion recovery and T2 images and low on the T1-weighted images noted in the cerebral gray white matter junction as well as the basal ganglia bilaterally. The brain stem and cerebellum were relatively spared. Postcontrast images revealed no significant enhancement (Figure 1).

The above-described findings from MRI of the brain were suggestive of acute disseminated encephalomyelitis (Figure 1). The patient was started on pulse steroid therapy (20 mg/kg/d) for 5 days. She showed no improvement and was still ataxic and irritable with excessive salivation. The presentation with the MRI finding and the lack of clinical improvement led to the

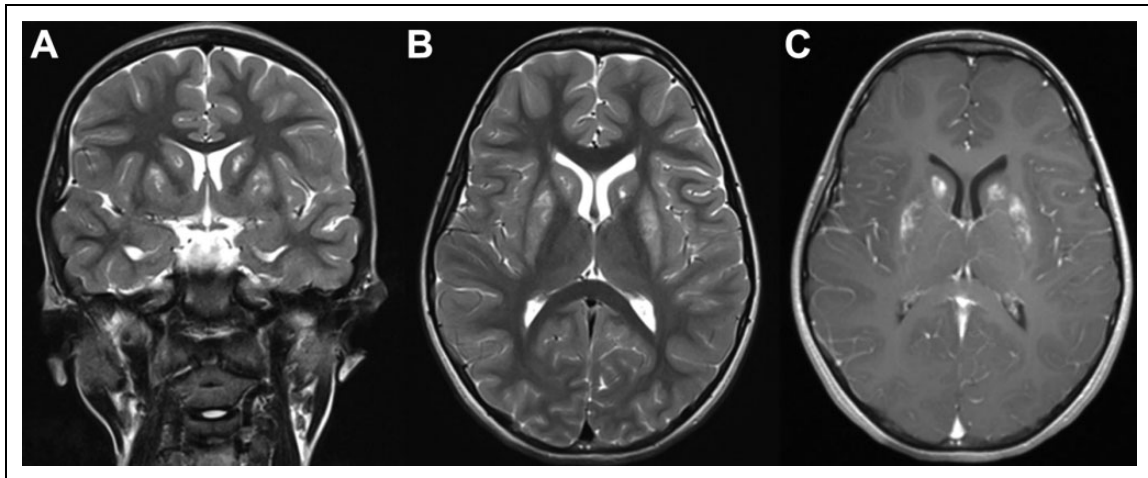


Figure 2. Magnetic resonance imaging (MRI) of the brain with T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences showing high signal intensity in the basal ganglia at the time of the biotin-thiamine-responsive basal ganglia disease (BTBGD) crisis at the age of 7 years (A, B, C).

suspicion of biotin-thiamine-responsive basal ganglia disease, and she was started empirically on 70 mg of oral biotin twice daily (5 mg/kg/d) and 100 mg of oral thiamine 3 times a day (20 mg/kg/d). Two days later, the patient showed marked improvement with no irritability, was active, and was smiling with no crying. A neurological examination showed only mild tremor and wide-based gait. The significant improvement was suggestive of biotin-thiamine-responsive basal ganglia disease. Therefore, genetic testing was sent for the mutation of the SLC19A gene, and she was discharged on 70 mg of oral biotin twice daily (5 mg/kg/d) and 100 mg of oral thiamine 3 times a day (20 mg/kg/d). Magnetic resonance imaging that was repeated 1 month after the patient started biotin and thiamin revealed the marked improvement of the previously noted white matter signal abnormality, along with improvement of the bilateral basal ganglia, but still a certain amount of residual signal alteration was present with no new changes, and genetic testing confirmed homozygous missense mutation in exon 5 of the SLC19A3 gene (c.1264 A>G [p.T422A]).

The patient was followed in the neurology and metabolic clinics, and she was compliant with the medications. Her ataxia and salivation improved gradually within a couple of months, and her parents noticed a decrease attention and self-stimulatory behaviors. Upon further follow-up, the patient appeared to be neurologically and developmentally normal apart from showing some signs of learning disability although full psychiatric assessment was not done.

Follow-Up

When the patient turned 7 years old, and for social reasons, her parents stopped giving her medications. Two weeks later, the patient began to have tremor in both hands with an unsteady gait, so the family resumed the medications: 100 mg of oral biotin twice a day (10 mg/kg/d) and 400 mg of oral thiamin twice a day (40 mg/kg/d). Even after resuming the medications

for 3 days, however, the patient remained symptomatic. Therefore, she was brought to the emergency department with drooling, a visual disturbance, ataxia, and the inability to walk.

A neurological examination showed her to be fully conscious with marked dystonia of the upper and lower extremities. Rigidity, diffuse weakness muscle power 3/5, and brisk deep tendon reflex were also found. She also had significant upper and lower limb tremor with dysmetria. She was admitted with the suspicion of biotin-thiamine-responsive basal ganglia disease because of discontinuation of medications.

Magnetic resonance imaging showed abnormal signal intensities, and compared with previous MRI studies, a redemonstration of signal abnormalities was found in the basal ganglia region bilaterally with the development of tiny cystic changes representing necrosis (Figure 2).

The patient's condition was managed with 400 mg of intravenous thiamine twice daily (40 mg/kg/d) and 100 mg of oral biotin twice daily (10 mg/kg/d). Three days later, the patient showed very minimal improvement, so her thiamine was increased to 400 mg intravenously 3 times a day (60 mg/kg/d). After 48 hours, she showed gradual improvement and was discharged 1 week later with no more drooling, with residual mild upper and lower limb tremor, and with right lower limb dystonia. She was discharged on 400 mg of oral thiamin twice a day (40 mg/kg/d) and 100 mg of oral biotin twice a day (10 mg/kg/d).

The patient was followed in the neurology clinic 6 months later, at which time she was complaining of slow yet clear writing. Her full neurological examination was normal with no tremor, and her dystonia had disappeared.

Discussion

Biotin-thiamine-responsive basal ganglia disease is a rare disorder that requires a high level of suspicion to diagnose. There are multiple mutations responsible for this disease, with

homozygous missense mutation in exon 5 of the SLC19A3 gene (c.1264 A>G [p.T422A]) being the most common and is the founder mutation in Saudi Arabia, since almost all biotin-thiamine-responsive basal ganglia disease cases with Saudi origins has this mutation.¹ As reported in the previous literature, a patient with biotin-thiamine-responsive basal ganglia disease can have a good outcome if the disease is diagnosed early and if the patient is started on biotin and thiamin with good compliance.¹

Still, the last recommendations are the continuation of both biotin and thiamine, even though the latest study showed no difference in disease outcome in a patient who receives thiamine and biotin compared with thiamine alone over a 30-month period.⁴

Our patient showed good response to early treatment; however, she experienced a relapse after the discontinuation of the supplement. Unfortunately, no clear guideline exists in the literature regarding the management of a relapse or severe crisis. Our patient didn't improve after resuming her regular doses, which suggests that during crisis a much higher dose should be given. Therefore, we had to have her thiamine dose increased to achieve remission. She ultimately recovered from tremor, ataxia, and dystonia. However, she continues to have slow fine motor skills and a possible learning disability, and she will need to undergo a proper psychiatrist evaluation for any psychological complications. Further follow-up revealed the return of her neurological condition to her baseline with no apparent longtime affection of this crisis.

We recommend that patients experiencing biotin-thiamine-responsive basal ganglia disease crises be treated with higher dosages of thiamine from the beginning. The exact dosing and duration required to treat the crisis is not yet clear. Thus, further studies are needed in this area.

Conclusion

Patients with biotin-thiamine-responsive basal ganglia disease should remain on lifelong treatment with thiamine and biotin. For those who present with acute relapses, we recommend inpatient treatment with high doses of intravenous thiamine

and oral biotin. Further clinical research is required to determine the optimal doses and durations.

Author Contribution

Both authors contributed to the conception of the idea, acquisition of the clinical data, drafting and revision of the manuscript.

Declaration of Conflicting Interests

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Ethical Approval

Ethical approval has been waived according to our hospital regulations as it is not required for case reports. Informed consent was obtained from the patient's parents.

References

1. Alfadhel M, Almunashri M, Jada H, et al. Biotin-responsive basal ganglia disease should be renamed biotin-thiamine-responsive basal ganglia disease: a retrospective review of the clinical, radiological and molecular findings of 18 new cases. *Orphanet J Rare Dis*. 2013;8:83.
2. Ozand PT, Gascon GG, Al Essa M, et al. Biotin-responsive basal ganglia disease: a novel entity. *Brain*. 1998; 121(Pt 7):1267-1279.
3. Zeng WQ, Al-Yamani E, Acierno JS, et al. Biotin-responsive basal ganglia disease maps to 2q36.3 and is due to mutations in SLC19A3. *Am J Hum Genet*. 2005;77(1):16-26.
4. Tabarki B, Alfadhel M, AlShahwan S, Hundallah K, AlShafi S, AlHashem A. Treatment of biotin-responsive basal ganglia disease: open comparative study between the combination of biotin plus thiamine versus thiamine alone. *Eur J Paediatr Neurol*. 2015; 19(5):547-552.
5. Alfadhel M, Al-Bluwi A. Psychological assessment of patients with biotin-thiamine-responsive basal ganglia disease. *Child Neurol Open*. 2017;4:2329048X17730742.