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Case report

Biotin-thiamine-responsive basal ganglia disease: A case report[☆]

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ABSTRACT

Biotin-Thiamine-Responsive Basal Ganglia Disease is an extremely rare autosomal recessive neurometabolic disorder characterized by recurrent waxing and waning episodes of subacute encephalopathy and seizures. High dose biotin and thiamine administration has been shown to improve symptoms within days, and the symptoms may reappear rapidly if supplementation is discontinued. Here we present a case of a 20-year-old male with classical clinical and imaging findings of Biotin-Thiamine-Responsive Basal Ganglia Disease, with a 12-year delay in diagnosis, finally diagnosed after presenting at our institution based on imaging and subsequent reexamination of exome sequencing. In this report, we review the classic imaging findings in this disease and examine why making the diagnosis can be extremely challenging due to its wide differential. Both clinically and radiographically, this condition demonstrates significant overlap with a vast array of disease entities, ranging from viral or autoimmune encephalitis to metabolic disorders. Finally, we discuss the various negative prognostic predictors described in the literature, several of which were observed in this patient's clinical course.

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Biotin-thiamine-responsive basal ganglia disease (BTBGD) is an extremely rare autosomal recessive neurometabolic disorder characterized by recurrent waxing and waning episodes of subacute encephalopathy and seizures [1,2]. The disease is linked to genetic defects in *SLC19A3* gene, which encodes a second thiamine transporter [3]. The severity of disease ranges from normal to severely affected, and the disease course of affected individuals is highly variable as far as age

of onset, treatment response, and outcomes [4]. High dose biotin and thiamine administration has been shown to improve symptoms within days, and the symptoms may reappear rapidly if supplementation is discontinued [1,4]. Here we present a case of a 20-year-old male with classical clinical and imaging findings of Biotin-Thiamine-Responsive Basal Ganglia Disease, diagnosed at our institution based on imaging and subsequently confirmed with genetic testing.

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Case report

In April 2021, a 20-year-old male presented to our institution with 5 days of ongoing generalized tonic-clonic seizures. He had been followed since age 8 at various institutions for a history of recurrent waxing and waning episodes of neurologic symptoms including seizures, choreoathetosis, kinesigenic dystonia, truncal hypotonia, apraxia, and ataxia. Since his initial presentation he had undergone neurologic imaging numerous times, with prior brain MRIs typically demonstrating grey matter involvement with transient bilateral basal ganglia and cortical hyperintensities.

Upon first presentation of symptoms at age 8, the patient was initially admitted for a presumed viral encephalitis, managed conservatively with spontaneous improvement and subsequent discharge. However, within 1 month he was readmitted with recurrent and progressive symptoms. Brain MRI imaging at these admissions revealed diffuse, bilateral signal abnormalities of the cortex and basal ganglia. Lumbar punctures were negative multiple times, as were extensive infectious and rheumatologic workups. The patient was empirically treated for acute disseminated encephalomyelitis, but did not have significant improvement on pulse dose steroids. He eventually showed gradual resolution of symptoms, but it remained unclear whether this was due to the natural disease course or a response to empiric therapies. Since these initial hospitalizations, the patient had been readmitted numerous times, ranging from every few months to biennially, with a similar constellation of neurologic symptoms. Mitochondrial panels and muscle biopsies obtained over time were negative. While the underlying etiology was unknown during this period, patient was diagnosed with seizure disorder managed with long-term levetiracetam.

Upon presentation to our institution at age 20 with ongoing generalized tonic-clonic seizures, the patient again underwent extensive neurologic workup. A cerebral angiogram was performed, demonstrating mild nonspecific hyperemia, but no areas of luminal irregularity or stenosis to suggest vasculitis. A subsequent brain biopsy was nondiagnostic, with pathology negative for vasculitis, acute infection, or demyelinating process. Large volume lumbar punctures revealed normal white blood cell counts, normal protein and glucose levels, and cultures negative for bacterial, mycobacterial, and fungal organisms.

MRI of the brain obtained during the early hospital course revealed extensive FLAIR hyperintense signal in the bilateral basal ganglia, medial thalami, periaqueductal gray, asymmetric multifocal areas of bilateral cerebral cortex, and the cerebellum (Figs. 1A and B). Majority of these areas showed associated restricted diffusion (Fig. 1C). Post-contrast images demonstrated extensive sulcal leptomeningeal and basal ganglia enhancement (Fig. 1D). Findings were described as corresponding to a broad differential including toxic, metabolic, and autoimmune etiologies.

While admitted, the patient continued to clinically decline, with encephalopathy, obtunded mental status, hyperthermia, and acute hypercapnic respiratory failure. After 2 weeks of ventilator dependency, he underwent tracheostomy and gastrostomy tube placement. Our neuroradiology depart-

ment was re-consulted by the primary team for a multidisciplinary discussion regarding the patient's clinical course, in-hospital workup, and the imaging findings. The possibility of BTBGD was proposed as a differential consideration.

Reanalysis of previous exome sequencing initially performed in 2012 was revealing for mutation in *SLC19A3*, a gene abnormality associated with BTBGD, with a phenotypic match to his clinical course. Treatment was initiated with high-dose thiamine and biotin, and the patient demonstrated continually improving alertness on exam. Repeat MRI of the brain towards the end of the hospital course revealed interval decrease in the degree of FLAIR hyperintensity involving the bilateral basal ganglia and cerebral cortex, with subtle associated restricted diffusion, decreased from prior (Fig. 2). He was subsequently discharged to a subacute care facility. Unfortunately, about a month after discharge, the patient's father reported in a follow-up phone call that the patient had passed away at an outside facility due to unknown causes.

Discussion

BTBGD is an autosomal recessive neurometabolic disorder characterized by subacute encephalopathy, dystonia, seizures, and dysarthria, often associated with febrile illness [1,2]. The disease was first described by Ozand et al. in 1998 as biotin responsive basal ganglia disease (BBGD), in a case series of 10 patients of Saudi, Yemeni, and Syrian ancestry [5]. Subsequently, while the majority of reported cases describe patients from Saudi Arabia, several have been reported in patients of other ethnicities including Canadian, Indian, Japanese, Mexican, and western European origin [1,2,6]. In 2005, BTBGD was linked to genetic defects in *SLC19A3* gene, which encodes a second thiamine transporter (hTHTR2) [3]. Other conditions have also been linked to *SLC19A3* mutations including Leigh-like syndrome in infants and Wernicke's-like encephalopathy in young adults [4,6]. The mutation has variable penetrance, with clinical features ranging from normal to severely affected, and the disease course of affected individuals is highly variable as far as age of onset, treatment response, and outcomes [4]. Classically, high dose biotin and thiamine administration may improve symptoms within days, and the symptoms may reappear within 1 month if supplementation is discontinued [1,4].

The precise mechanism by which biotin supplementation improves symptomatology in BTBGD is unknown, as biotin is not a substrate for the thiamine transporter hTHTR2[4]. Biotin is a cofactor for several metabolic enzymes, assisting in the transfer of bicarbonate to a substrate generating a carboxyl product [4]. However, it is hypothesized that the biotin and thiamine transporters in the basal ganglia are closely associated structurally similar [1,4]. *In vitro* studies have suggested that, in patients with BTBGD, administration of high doses of both vitamins can act synergistically to increase expression of *SLC19A3*, thereby restoring some function of the mutated receptor [7]. In a retrospective cohort study of 18 patients with BTBGD, a third of the patients had recurrent acute encephalopathy crises when treated with biotin alone, but after

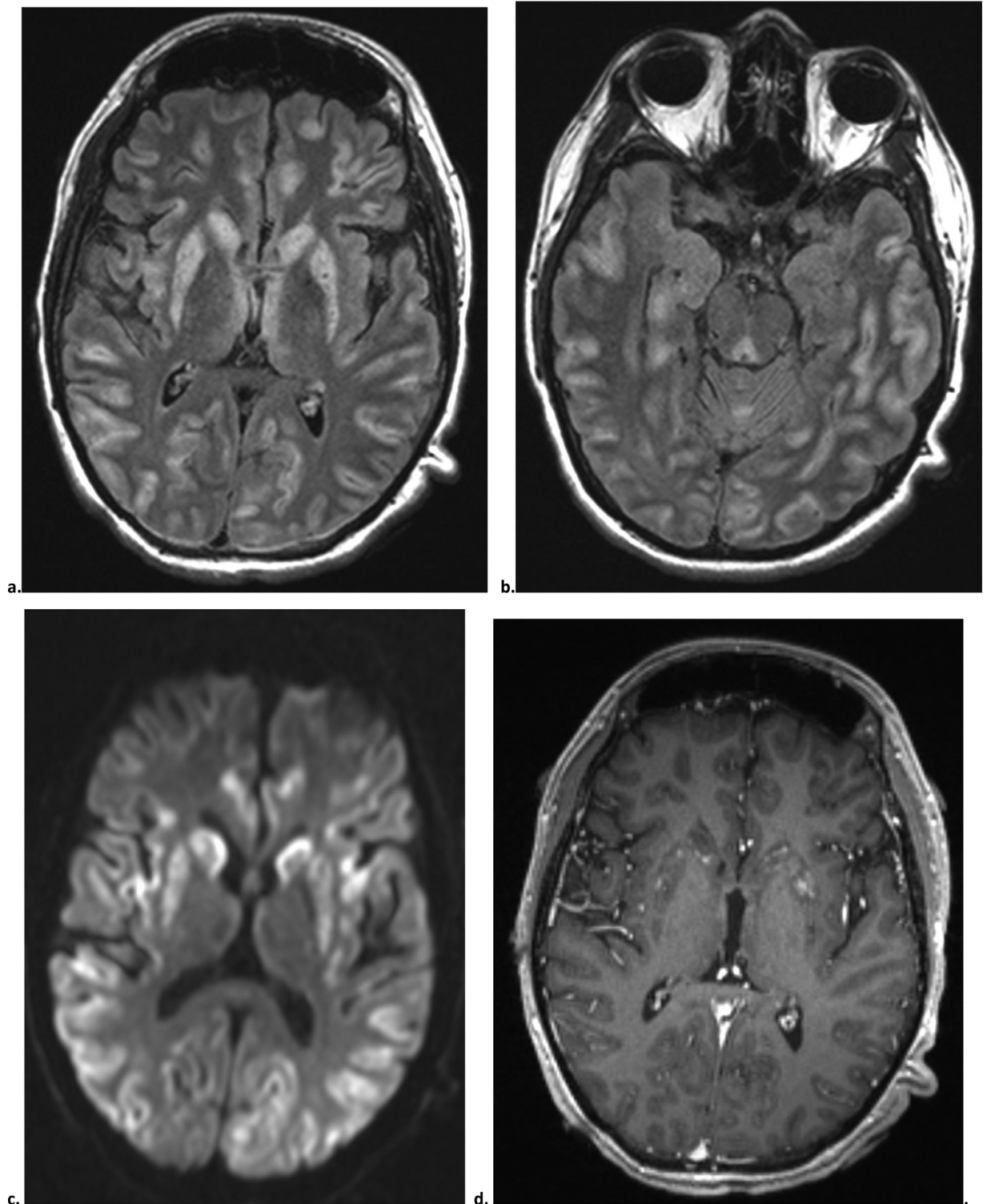


Fig. 1 – Axial magnetic resonance images of the brain during acute encephalopathic phase. (A) FLAIR sequence images demonstrate symmetric signal hyperintensity of the caudate, putamen, and medial thalami bilaterally, along with asymmetric scattered cortical hyperintensities. (B) FLAIR sequence at level of midbrain demonstrates increased signal of the periaqueductal gray matter. (C) Diffusion-weighted images show symmetric restricted diffusion in the bilateral basal ganglia corresponding to areas of increased FLAIR signal. (D) Post-contrast images demonstrate heterogeneous enhancement of bilateral caudate and putamen.

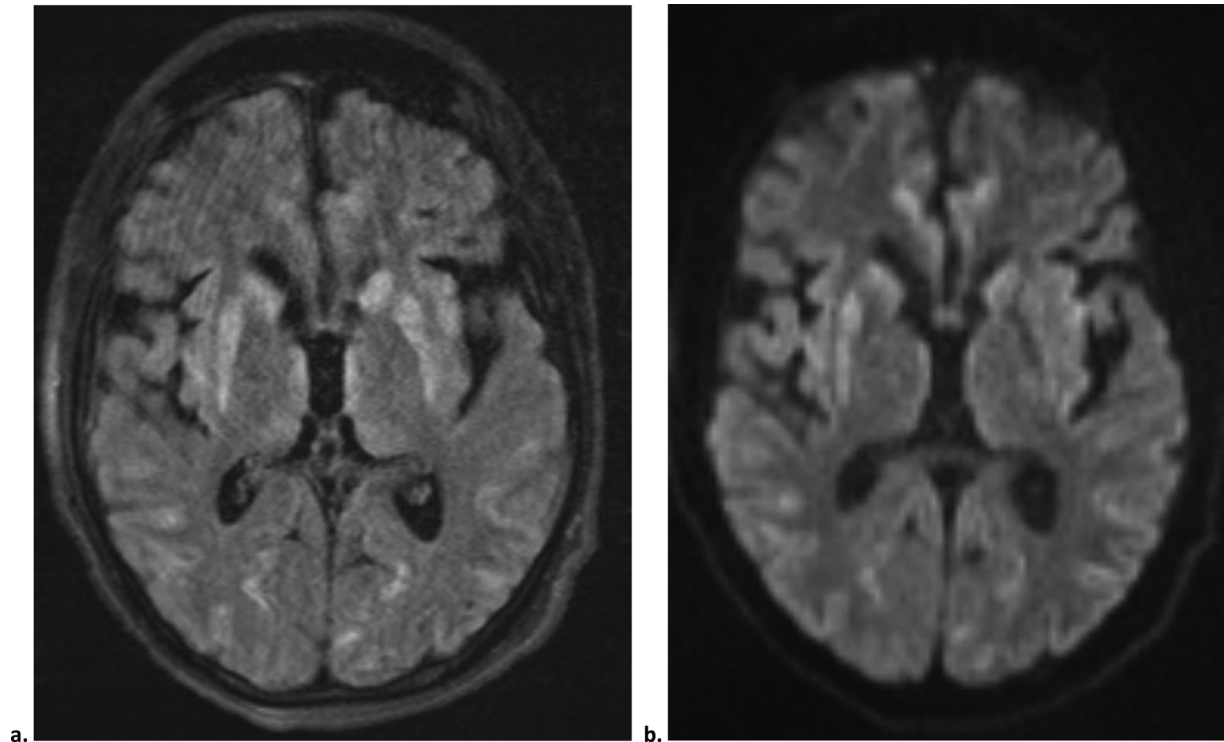


Fig. 2 – Axial magnetic resonance images of the brain near end of hospital course. (A) Compared to Figure 1A, there is decreased FLAIR hyperintensity involving bilateral ganglia. (B) Diffusion-weight images demonstrates mild residual restricted diffusion in the bilateral basal ganglia, decreased compared to prior exam.

the addition of thiamine, there were no further recurrences, further supporting the need for both biotin and thiamine supplementation in this disease process [1].

Classic imaging findings in BTBGD are bilateral increased T2 signal intensity in the basal ganglia with swelling during acute phase and atrophy and necrosis of the basal ganglia in the chronic phase [1,5]. In 2014 Kassem et al. performed a retrospective review of neuroimaging features in 15 patients with genetically proven BTBGD [2]. In their study, all patients demonstrated bilateral and symmetric lesions in the caudate heads with complete or partial involvement of the putamen, and sparing of the globus pallidi in all patients. Furthermore, in 80% of patients, additional discrete abnormal signal changes were observed in the cortical and subcortical white matter regions, and the medial dorsal nuclei of the thalami. The cerebellum along the cerebellar cortex and vermis was involved in only 2 of the 15 patients [2]. Following treatment with biotin and thiamine, there was development of atrophy and necrosis of the basal ganglia observed in all cases. However, the abnormal signal intensity of the caudate and putamen persisted in all patients. Diffuse cortical and subcortical white matter and the infratentorial involvement has also been reported in several other studies [1,4]. Our patient demonstrated extensive FLAIR hyperintense signal in the bilateral basal ganglia, medial thalami, multifocal areas of bilateral cerebral cortex, and the cerebellum, consistent with the findings described in the literature.

As was the case with our patient, despite the presence of classical radiological changes, there may be a delay in di-

agnosis for many years in patients with BTBGD, likely due in part to the rarity of this disease, along with an extensive differential diagnoses for bilateral basal ganglia T2 hyperintensity on MRI. One of the top differential considerations in BTBGD is viral encephalitis, particularly Epstein-Barr virus which also demonstrates multifocal cortical, subcortical, and bilateral deep grey matter T2-FLAIR hyperintensities [8]. Autoimmune-mediated etiologies of encephalitis can also present with bilateral basal ganglia involvement, however some potentially helpful distinguishing features include cortical thickening and involvement of mesial temporal lobes and limbic systems [8,9]. Another important differential consideration is mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), which clinically presents very similarly to BTBGD with a relapsing-remitting course, seizures, encephalopathy. MR findings in MELAS tend to resemble multifocal predominantly cortical ischemic insults or stroke-like lesions of various ages, frequently in non-vascular territories, often with subsequent development of brain atrophy [8,10]. Stroke-like lesions most frequently occur in the temporo-occipital region, although frontal and parietal regions can be involved [11]. Basal ganglia involvement in MELAS typically manifests as chronic calcifications, although small lacunar infarcts may be present [11]. Diagnosis can be made using a mitochondrial panel on peripheral blood sample. In October 2020, Mohammad et al. completed an international multicenter cohort study retrospectively examining 305 MRI scans of children with bilateral basal ganglia abnormalities, with the aim of recognizing clusters of neu-

roimaging patterns to guide clinicians in differentiating conditions [8]. This study established 4 distinct clusters: Cluster 1) T2-weighted hyperintensities in the putamen; Cluster 2) T2-weighted hyperintensities or increased MRI susceptibility in the globus pallidus; Cluster 3) T2-weighted hyperintensities in the globus pallidus, brainstem and cerebellum with diffusion restriction; Cluster 4) T1-weighted hyperintensities in the basal ganglia. BTBGD was categorized as a Cluster 1 diagnosis, a group comprised primarily of metabolic disorders and inflammatory conditions of both infectious and autoimmune etiology. Cluster 1 etiologies were found to almost always spare the globus pallidi, again consistent with the results from Kassem et al. and with the findings in our patient case [2,8]. In the setting of conditions with bilateral basal ganglia abnormalities, clustering of neuroimaging patterns this way may help to narrow the differential diagnosis and guide diagnostic workup [8].

Several studies to have shown that failure to initiate therapy with biotin and thiamine early in the course of BTBGD results in a negative clinical outcome [1,4]. Other reported poor prognostic factors include early disease onset, missed or delayed diagnosis, involvement of other organ systems including respiratory failure or rhabdomyolysis, and severe neurological deficit or marked radiological abnormalities at the time of diagnosis and treatment initiation [4]. In a 2013 retrospective series of 18 patients, 8 patients with delayed diagnosis had mild to moderate neurological deficits, while 7 patients who were diagnosed immediately achieved normal development [1]. The same study also reported a correlation between number of acute encephalopathic episodes and clinical outcomes, nothing that all children with normal outcomes had only 1 acute event.

In this report, we have described a case of BTBGD in a patient with a 12-year course of hospitalizations for seizure disorder with recurrent encephalopathic episodes, with extensive workup including brain biopsy, serum and CSF testing, negative mitochondrial panel, prior exome sequencing, and multiple MRIs obtained over 12 years showing diffuse bilateral cortical and deep grey matter T2-FLAIR hyperintensities. In this case, BTBGD was proposed a diagnostic possibility at age 20, several years after disease onset, prompting reanalysis of exome sequencing which ultimately clarified the underlying etiology. In our patient, the imaging findings were consistent with the Cluster 1 neuroimaging pattern established by Mohammed et al., with bilateral caudate and putamen involvement and sparing of the bilateral globus pallidus. Following initiation of combination therapy with biotin and thiamine, the patient had improvement in both his neurologic exam and his radiologic findings, with decreased bilateral basal ganglia and cortical signal abnormalities, consistent with the expected clinical course described in existing literature. However, our patient's 12-year-long disease course featured several negative prognosticators which likely contributed to the his overall poor clinical outcome, including early age of onset, several year delay in diagnosis resulting in delayed initiation of biotin and thiamine supplementation, multiple acute encephalopathic episodes, significant neurological and radiologic abnormalities at the time of diagnosis, and involvement of additional organ systems requiring intensive care and intubation.

Conclusion

BTBGD is an extremely rare inherited condition and a challenging diagnosis to make due to a nonspecific clinical presentation of encephalopathy and seizures and an extensive imaging differential for bilateral basal ganglia and cortical T2-hyperintensities. This report demonstrated a case of a 12-year delay in diagnosis of a patient with BTBGD, leading to late initiation of therapy and a severe and complicated disease course. It is important for neurologists and radiologists to be aware of and consider this rare disease entity in the appropriate context, as prompt diagnosis and early initiation of treatment can have a significant positive impact on patient outcomes.

Patient consent

Informed consent was not required for the preparation of this imaging-based case report as all brain MRI images and clinical data are completely anonymized with no patient identifiers in any part of the manuscript. Furthermore, the patient had passed away at the time of writing this case report.

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