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Case Report

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Biotin-thiamine-responsive basal ganglion disease: Outcome after use of high and low dose of biotin and thiamine

Shabir Ahmed, MD, Amal Al Qassimi, MD

[1]*Assistant consultant pediatric neurology, King Saud Medical City Riyadh, Saudi Arabia*
[2]*Consultant and Head of department Pediatric Neurology*

***Corresponding author:** Amal Al Qassimi, MD, Department of Pediatric Neurology, King Saud Medical City Riyadh Postal code 11654, Saudi Arabia.

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Abstract

***Background:** Biotin-thiamine-responsive basal ganglion (BTBGD) is an autosomal recessive neurometabolic disorder associated with pathogenic variants in SLC19A3 gene. The clinical presentation includes subacute encephalopathy (e.g. Confusion, dysphagia, dysarthria, and seizures), which respond very well to early treatment with thiamine and biotin.*

In our case, patient presented with acute encephalopathy, ataxia, dystonia, dysarthria later quadriparesis. The baseline MRI Brain demonstrated abnormal signal intensity in cerebral cortex both in supra and infratentorial areas and basal ganglion. Once diagnosis of biotin-thiamine-responsive basal ganglion was made, patient was started on high doses of oral thiamine and biotin. Genetic Testing demonstrated pathogenic variant in SLC19A3 gene. After start of treatment with oral biotin and thiamine patient started improvement in clinical course within days. After improvement patient was discharged home and advised to follow up in pediatric neurology clinic. In follow up patient showed both clinical and radiological improvement. Family screening was done showed both parents are carriers and one sister has similar mutation but all of them were asymptomatic.

***Conclusion:** BTBGD is an extremely rare inherited condition and a challenging diagnosis to make due to nonspecific clinical presentation of encephalopathy and seizures. Early treatment and diagnosis affect the outcome of disease.*

Keywords: Biotin-Thiamine-Responsive Basal Ganglion Disease, Slc19a3 Mutation, Outcome After Use Of High Versus Low Dose Of Thiamine And Biotin.

Introduction

Biotin-thiamine-responsive basal ganglion 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 biotin and thiamine is discontinued or dose of medication is decreased [1,4]. Here we present case of a 9 year and 10 months old with classical clinical and imaging findings of Biotin-Thiamine-Responsive Disease, diagnosed at our institution based on imaging and subsequently confirmed with genetic testing.

Case Report

9 year and 10 months old male presented to our institution with acute encephalopathy, ataxia, dysarthria.

Upon presentation of symptoms, the patient was initially managed as autoimmune encephalitis, managed conservatively and received intravenous immunoglobulin. During hospital stay we involved subspecialities like infectious department and Pediatric Rhematology. Autoimmune, infectious and vascular causes were ruled out. MRI brain was done as shown in Fig.1 (images A and B) that revealed extensive cortical involvement in supra and infratentorial areas with involvement of basal ganglion and thalami. Based on Clinical features and MRI imaging findings as shown in Figure 1 (A and B images), we suspect patient has Biotin thiamine responsive basal ganglion. Treatment was initiated with high-dose oral thiamine and biotin. Exome sequencing was send during hospital admission for mutation in SLC19A3, a gene abnormality associated with BTBGD, with phenotype match to

his clinical course. After treatment was initiated with biotin and thiamine patient demonstrated continually improving alertness, ataxia and other symptoms and signs. Later exome sequencing showed homozygous mutation in SLC19A3 gene so diagnosis of BTBGD was confirmed. Once patient showed improvement in his clinical findings, he was discharged home with follow up with pediatric neurology. This patient has multiple visits to our clinic he is improving with time, once we tried to decrease dose of oral biotin and thiamine, his clinical condition started to worsen like tremor, ataxia and dystonia, then again we shifted to high doses of biotin and thiamine. After resuming high doseof medications his clinical conditions started improving. The MRI Brain was repeated in pediatric neurology clinic as shown in Fig. 1 (images C and D) that showed almost complete resolution of the superficial extensive cortical lesions in the supra and infratentorial brain and brain stem. Basal ganglion hyperintensities also significantly improved.

Family study and screening was done revealed another sibling affected, both parents are carriers of disease. Sibling that has positive mutation is 2 year and 5 months old and and has positive homozygous mutation in SLC19A3 gene. Genetic diagnosis of autosomal recessive thiamine metabolism dysfuntion syndrome 2 was diagnosed in this case. This child has failure to thrive and central hypotonia that probably was not associated with BTBGD. We did MRI brain for this child also but it was normal. She was also started on oral thiamine and biotin as prophylaxis.

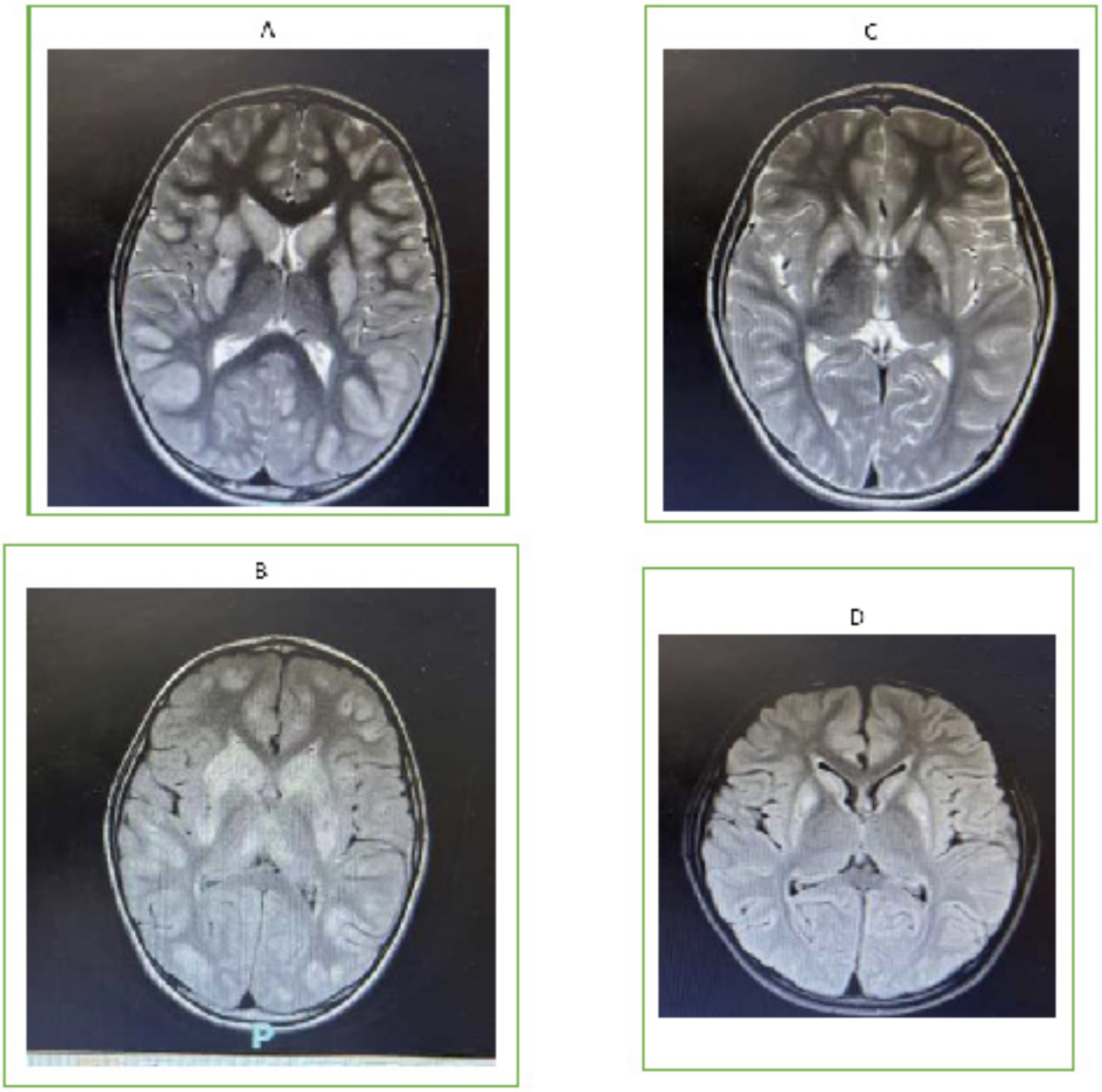

Figure 1: Axial magnetic resonance images of the brain during acute encephalopathic phase, T2 and FLAIR sequence images (A and B) demonstrate symmetric signal hyperintensity in cortical areas, cerebellar hemispheres, central part of thalami and basal ganglion. Control MRI Brain repeated revealed as shown in FLAIR sequence and T2 sequence image (C and D) almost complete resolution of superficial cortical lesions and brain stem lesions. Basal ganglion hyperintensities also significantly improved.

Discussion

Biotin-thiamine-responsive basal ganglion disease is autosomal recessive neurometabolic disorder characterised by subacute encephalopathy, dystonia, seizures, dysarthria, often associated with febrile illness [1,2]. Biotin-Thiamine deficiency is very rare disease , in many previous research articles comparison of high versus low dose of thiamine and biotin was made for treatment it was found that high dose is very effective for treatment of disease than low dose of thiamine and biotin [12]. In our case patient also showed similar scenario , he showed significant improvement when he was treated with high doses of thiamine and biotin than low doses. The disease was first described by Ozand et al.in 1998 as biotin responsive basal ganglion disease, in case series of 10 patients of Saudi, Yemini, and Syrian ancestry [5]. Subsequently, while the majority of reported cases were reported from Saudi Arabia, several have been reported cases from 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 (THTR2) [3].

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 functions of the mutated receptor [7].

Classic imaging findings in BTBGD are bilateral increased T2 signal intensity in the basal ganglion with swelling during acute phase and atrophy and necrosis of the basal ganglion in the chronic phase [1,5]. In 2014 Kassem et al. performed a retrospective review of of neuroimaging features in 15 patiens with genetically proven BTBGD [2]. In this 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 percent 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 out of patients [2]. Our patient demonstrated extensive FLAIR and T2 hyperintense signal in the bilateral cerebral hemisphere, cerebellar hemisphere, bilateral basal ganglion and central thalami bilaterally.

One of the top differential considerations in BTBGD is viral encephalitis, particularly Ebstein-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 ganglion involvement, however some potentially helpful distinguishing features include cortical thickening and involvement of mesial temporal lobes and limbic system [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. MRI findings in MELAS tend to resemble with stroke like episodes of various ages, frequently in non-vascular territories, often with subsequent development of brain arophy [8,10]. Stroke like lesions most frequently occur in temporo-occipital region, although frontal and parietal regions can be involved [11]. Basal ganglion involvement in MELAS typically manifests as chronic calcifications, although small lucunar infarts may be present [11].

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 our report, we have described a case of BTBGD in a patient 9 year and 10 months old who was admitted with acute encephalopathy, dystonia, ataxia and dysarhria. We did extensive work up for him including CSF testing, basic work up, MRI brain and spine with contrast, anti-dsDNA, ANA and serum ammonia and lactate. Whole exome sequencing was also send. In this case, BTBGD was proposed a diagnostic possibility and patient was started on high dose of oral thiamine and biotin. MRI Brain findings were consistent with BTBGD with involvement of basal ganglion and cortical involvement. Later diagnosis in our case was confirmed by exome sequencing which showed homozygous mutation in SLC19A3 GENE. Following initiation of combination therapy with biotin and thiamine the patient had improvement in both his neurological exam and his radiologic findings, with decreased bilateral cortical and basal ganglion high signal abnormalities, consistent with the expected clinical course described in existing. litrature

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 imagining differential for bilateral basal ganglion and cortical T2-hyperintensities. This report demonstrated a case of a 9 year and 10 months old who presented with acute encephalopathy, ataxia and dystonia. He was treated with high doses of thiamine and biotin with good response after diagnosis was made by clinical and radiological features and confirmation of diagnosis was later made of exome sequencing.

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