Review Article

# Biotin-Thiamine-Responsive Basal Ganglia Disease in Children: A Treatable Neurometabolic Disorder

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## Abstract

Biotin-thiamine-responsive basal ganglia disease is a rare, autosomal recessive, treatable, neurometabolic disorder associated with biallelic pathogenic variations in the *SLC19A3* gene. The condition may present as an early-childhood encephalopathy, an early-infantile lethal encephalopathy with lactic acidosis, with or without infantile spasms, or a late-onset Wernicke-like encephalopathy. The key radiological features are bilateral, symmetrical lesions in the caudate, putamen, and medial thalamus, with variable extension into the brain stem, cerebral cortex, and cerebellum. Treatment is life long and includes initiation of high dose biotin and thiamine. Genetic testing confirms the diagnosis. The prognosis depends on the time from diagnosis to the time of vitamin supplementation. The genotype-phenotype correlations are not clear yet, but the early infantile phenotype portends a poorer prognosis. We provide a brief overview of the disorder and emphasize the initiation of high-dose biotin and thiamine in infants and children with unexplained encephalopathy and basal ganglia involvement.

**Keywords:** Basal ganglia, biotin, encephalopathy, IEM, metabolic, SLC19A3, thiamine

## Introduction

Biotin-thiamine-responsive basal ganglia disease (BTBGD) is a rare, autosomal recessive, treatable, neurometabolic disorder associated with biallelic pathogenic variations in the solute carrier family 19 member 3 *(SLC19A3)* gene.[1] Ozand *et al*. first described the entity in 1998 as a childhood encephalopathy responsive to biotin and named 'biotin-responsive basal ganglia disease'.[2] Since then, the disorder has come a long way with expansion of phenotypic subtypes and age at presentation, the discovery of underlying genetic variations, pan-ethnic distribution, and therapeutic response to high-dose biotin and thiamine. The terminology has subsequently been changed to include biotin and thiamine responsiveness to denote this group of disorders.[3] Overall, a birth prevalence of 1 in 215000, and a carrier frequency of 1 in 232 persons in the general population have been estimated for all BTBGD phenotypes.[4] Based on the genetic screening of healthy newborn babies, a carrier frequency of 1 in 500 individuals and a prevalence of one in millions has been estimated in the Saudi population.[5] The disorder is probably underdiagnosed and may be missed as Leigh syndrome, mitochondrial disease, or infection-associated demyelination syndromes. When untreated or inadequately treated, the condition presents with progressive neurodegeneration and death. In this review, we provide a brief overview of the BTBGD associated with *SLC19A3* variations to sensitize the readers to this eminently treatable neurometabolic disorder. We also emphasize the initiation of high-dose biotin and thiamine in infants and children with encephalopathy and basal ganglia involvement.

## Pathophysiology of Thiamine-based Neurological Disorders

Thiamine, commonly known as vitamin B1 or aneurine, is a water-soluble, essential vitamin for humans. Thiamine pyrophosphate (TPP) is the most metabolically active form of thiamine in the body.[1] Table 1 provides a list of enzymes where thiamine is a cofactor and the disorders associated with thiamine metabolism.[6,7] The human *SLC19A3* gene has been mapped to chromosome 2q36.3 in 2005.[8] It encodes a second human thiamine transporter.[9] In *SLC19A3*-associated disorders, the mutated transporter is either incorrectly localized in the cells or has a reduced affinity for thiamine, or fails to up-regulate the gene expression during periods of metabolic stress, thus restricting the transport of thiamine into the cells.[10] When given in high doses, the increased concentration of thiamine in the blood probably overcomes the receptor block.[11] As biotin is not a substrate for the thiamine transporter, the role of

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**Table 1: The enzymes and common disorders associated with thiamine in humans[1]**

| The key enzymes where thiamine acts as a cofactor |
|---|
| Cytoplasm |
| Transketolase enzyme of the pentose phosphate pathway |
| Mitochondria |
| Pyruvate dehydrogenase complex (conversion of pyruvate into acetyl-CoA) |
| Oxoglutarate dehydrogenase complex (decarboxylation of α-ketoglutarate in Kreb's cycle) |
| Branched chain α-keto acid dehydrogenase complex (decarboxylation of branched, short-chain α-keto acids) |
| Peroxisomes |
| 2-hydroxyl acyl CoA lyase (fatty acid catabolism) |
| **Disorders associated with thiamine metabolism** |
| Acquired conditions associated with thiamine deficiency |
| Infantile beriberi |
| Wernicke's encephalopathy |
| Inherited disorders associated with thiamine dysfunction |
| Thiamine-responsive megaloblastic anemia syndrome (*SLC19A2*-associated thiamine metabolism dysfunction syndrome 1) |
| Biotin thiamine-responsive basal ganglia disease (*SLC19A3*-associated thiamine metabolism dysfunction syndrome 2) |
| *SLC25A19*-associated disorders |
| Thiamine metabolism dysfunction syndrome 3 (microcephaly Amish type) |
| Thiamine metabolism dysfunction syndrome 4 (bilateral striatal degeneration and progressive polyneuropathy type) |
| Episodic encephalopathy phenotype (TPK1-associated thiamine metabolism dysfunction syndrome 5) |

biotin supplementation is not clear.[12] One hypothesis suggests that the high dose biotin allows the accumulating pyruvate in thiamine deficiency to bypass the Kreb's cycle using the biotin-dependent pyruvate carboxylase enzyme.[13] This leads to the formation of oxaloacetate, which then enters the Krebs cycle instead of the acetyl-CoA and overcomes the metabolic block. The stress-induced upregulation of *SLC19A3* expression is an adaptive response and is lost in patients with BTBGD.[10]

## Clinical Features

Ozand *et al*. initially described the disorder in 1998 as early-onset (before four years of age), subacute encephalopathy, commonly triggered by a febrile illness or stress, seizures, external ophthalmoplegia, generalized secondary dystonia, quadriparesis, coma, and even death.[2] Over the years, several phenotypes have been associated with *SLC19A3*-related basal ganglia disease and thiamine responsiveness. Broadly, these can be divided into three forms based on their age of presentation:

- *Early childhood encephalopathy:* This is the classical form originally associated with pathogenic variations in *SLC19A3*. The disease typically presents in early or late childhood between 3 and 10 years of age with episodic encephalopathy, neuroregression, recurrent seizures (even status epilepticus), spasticity, severe extrapyramidal involvement (even status dystonicus), gait abnormalities, behavioral problems, and bilateral affection of the corpus striatum and cerebral cortex, with or without brain stem involvement.[3] The encephalopathy is often triggered by fever, metabolic stress, trauma, vaccination, or extensive exercise.[1,14] Seizures are often seen associated with the acute state but may also be the presenting symptom. Myoclonic jerks, infantile spasms, focal or generalized-onset motor seizures, generalized or focal status epilepticus, or a combination of several seizure types may be seen.
- *Early infantile form*: A more severe presentation has been described in early infancy that presents acutely as a rapidly progressing encephalopathy, seizures, lactic acidosis, neuroregression, poor response to thiamine, and premature death (often described as *early-infantile lethal encephalopathy*).[15,16] Some infants present with typical infantile spasms, severe psychomotor retardation, and progressive brain atrophy.[17] The latter condition is often described as a distinct phenotype under BTBGD. Sometimes, these patients present with infantile spasms in follow-up after an acute crisis. Epilepsy may evolve into Lennox-Gastaut syndrome with multiple seizure types.[18] The common feature in all these presentations is the bilateral basal ganglia lesions and an infantile-onset of severe neurological symptoms (as early as in the newborn period).[18]
- *Late-onset Wernicke-like encephalopathy:* often presents in the second decade with acute-onset neurological symptoms such as epilepsy, nystagmus, ophthalmoplegia, and ataxia. This presentation has been associated with compound heterozygous variations in the *SLC19A3* and shows a reversal of symptoms with high-dose thiamine supplementation.[19]

## Investigations

### Biochemical

BTBGD is not associated with a specific biochemical metabolite, which may clinch the diagnosis. As the underlying biochemical alteration is the failure of cellular energy mechanisms, it is often reflected as lactic acidosis in the

blood and urine. The excretion of organic acids in the urine in BTBGD is variable. It may reflect high concentrations of isobutyric, 2-hydroxy-isovaleric, 2,4-di-hydroxybutyric, 3-hydroxybutyric, α-keto glutaric, 2-hydroxyglutaric, glutaric, succinic, 2-ketoadipic and 4-hydroxy-phenyl lactic acids.[1,14] Plasma elevations of alanine, leucine, and isoleucine have also been reported.[11,16] Muscle histology and electron transport chain complex activities are normal.

### Thiamine assays

A normal concentration of total thiamine in the blood, and a low level of free thiamine in the cerebrospinal fluid and fibroblasts is seen.[11,20] Although not routinely available, the demonstration of decreased free thiamine in the cerebrospinal fluid has been suggested as a biomarker for diagnosis and monitoring of treatment.[1]

### Magnetic resonance imaging (MRI)

The key radiological feature is the presence of bilateral, symmetrical lesions in the caudate nuclei, putamen, and medial thalamus, with variable extension into the brain stem, cerebral cortex, and cerebellum [Figure 1a, 1b].[1] The swelling of the nuclei in the acute stage is due to cytotoxic edema and is reflected as diffusion restriction. Mixed diffusion abnormalities in the lesions may represent a combination of cytotoxic edema, vasogenic edema, and encephalomalacia.[4] The lesions may progress and lead to necrosis in the caudate and putamen. The involvement of globus pallidi and brainstem has been associated with a poor prognosis.[14] The cortical lesions typically involve the depth of the sulci.[15] There is an absence of significant contrast enhancement.[21] The early infantile form shows more extensive involvement. It has been categorized into an acute, post-acute, intermediate, and end-stage phase by Kevelam *et al*.[15] The acute swelling partially resolves and leads to rarefaction and cystic degeneration of deep grey nuclei and subcortical white matter. This is followed by progressive atrophy of the previously mentioned structures and cortical thinning in the intermediate and end-stage.[15]

Sparing of mammillary bodies and more extensive cortical involvement is seen in BTBGD compared to Wernicke's encephalopathy (acquired thiamine deficiency).[22,23] MR spectroscopy is non-specific. It often shows an increased lactate peak in the basal ganglia indicating energy failure and anaerobic metabolism during an acute crisis. Additionally, moderately decreased NAA to creatine ratio may be seen over the basal ganglia suggestive of neuronal loss. A pyruvate peak has been noted in the parietal white matter in patients with BTBGD akin to pyruvate dehydrogenase/succinate dehydrogenase deficiency. It reflects the role of thiamine as a cofactor for the mitochondrial enzyme pyruvate dehydrogenase.[4]

### Electroencephalograph

There are no pathognomonic patterns associated with BTBGD. The early infantile presentation has been reported to be associated with diffuse slowing, asymmetrical sleep spindles, generalized burst suppression, hypsarrhythmia, polyspike-wave complexes, and multifocal discharges.[18]

### Next-generation sequencing

Demonstration of biallelic pathogenic variations in the *SLC19A3* gene confirms the diagnosis and offers the chance for prenatal counseling. Loss-of-function mutations have been associated with defective transporter function. The majority of the described variations are missense, truncating (nonsense or frameshift), and rarely large deletions affecting the promoter region.[24] The genotype-phenotype and genotype-receptor function correlations are poor. Siblings from the same family may have different outcomes. A founder mutation in exon 5 (c. 1264 A > G [p.T422A]) has been described from Saudi Arabia.[3] As the disorder is pan-ethnic now, the ancestry is expanding, and more knowledge about the genetic footprint of the condition is expected in the future.

## Differential Diagnosis

Based on the above mentioned clinical, biochemical and radiological features, diagnostic criteria for *SLC19A3*-associated BTBGD have been suggested [Table 2].[1,14] We recommend

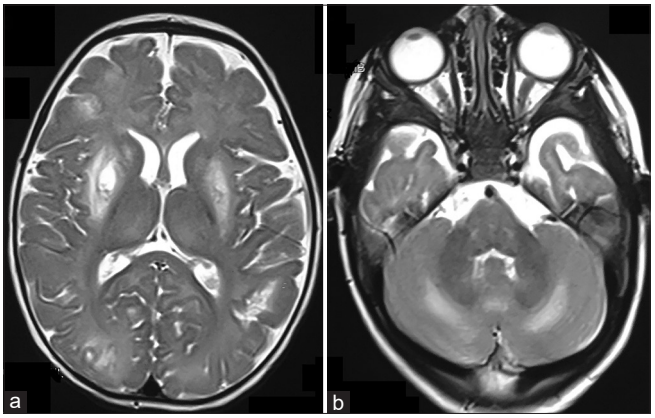


**Figure 1:** (a-b): Magnetic resonance imaging of the brain T2-weighted axial sections showing hyperintensities in bilateral caudate, putamen, cortical and subcortical white matter, with gliosis in the right putamen and left temporal lobe (B) bilateral involvement of the cerebellar hemispheres

**Table 2: Key features associated with BTBGD in children**

| |
|---|
| Acute, subacute or recurrent unexplained encephalopathy, coma or death |
| Movement disorder: dystonia, ataxia, severe cogwheel rigidity |
| Seizures, status epilepticus, infantile spasms |
| Bulbar dysfunction: dysphagia, dysarthria |
| External ophthalmoplegia |
| Spasticity |
| Consanguinity or family history |
| Triggers: non-specific febrile illness, mild trauma, surgery |
| Lactic acidosis with normal amino-acids, acyl carnitines and urinary organic acids |
| MRI pattern suggestive of Leigh syndrome or Wernicke's encephalopathy |
| Symmetrical involvement of caudate, putamen, cortical and subcortical areas, ventromedial thalamus, brain stem |
| Absence of mammillary body involvement |
| Clinical response to high dose thiamine supplementation |

that any combination of these features be used for suspecting *SLC19A3*-associated thiamine dysfunction syndrome. The acute encephalopathy due to thiamine metabolic dysfunction needs to be differentiated from infectious inflammatory central nervous system disorders (including demyelination, autoimmune, and vasculitis), toxic encephalopathies, and Wernicke encephalopathy. The inherited disorders that need to be excluded include organic acidemia, maple syrup urine disease, mitochondrial disorders, Wilson disease, Huntington disease, neurotransmitter disorders, and inherited dystonia.[22]

## Management

Timely recognition and management of the 'treatable' metabolic disorders improve the neurological outcomes, and the quality of life of the patients.[25] BTBGD is a potentially treatable neurometabolic disorder. Supportive care during an acute crisis of BTBGD includes intensive care support, maintenance of ventilation, treatment of seizures, empiric antibiotics until infectious trigger ruled out, and anti-dystonia measures. Fever down-regulates *SLC19A3* and may worsen the clinical condition; hence, temperature control should be aggressive.

Specific measures include the initiation of thiamine and biotin supplementation. The doses are higher than usually required for biotinidase deficiency and mitochondrial disorders. Biotin is initiated at 5-10 mg/kg/d, and thiamine at 10-40 mg/kg/d (300-900 mg).[22,26] Administration of high-dose thiamine restores its level in the cells and the cerebrospinal fluid, reduces the lactic acidosis, and limits cerebral edema and necrosis. Abrupt withdrawal of thiamine therapy has been associated with the recurrence of metabolic crises within 30 days.[19] During an acute crisis, the dose may be doubled and given intravenously. Intravenous dosing may be associated with transient local irritation or pruritus. Treatment is life-long. Certain drugs such as metformin, famotidine, chloroquine, and verapamil inhibit the thiamine transporter and should be avoided in these patients.[27] Stress and trauma can precipitate an acute crisis. Routine immunization is recommended.

## Outcome

The prognosis in BTBGD depends mainly on the timely diagnosis and initiation of vitamin supplementation.[28] Additional factors affecting the outcomes include the age of onset and the underlying genetic variation. The early childhood phenotype of BTBGD often shows clinical improvement and even remission with biotin and thiamine supplementation. However, the efficacy of these vitamins in early infantile forms is not established. Progressive brain atrophy and persisting infantile spasms often result in death by two years of age. The missense variations are associated with good response to biotin and thiamine, probably due to the residual activity of the defective receptor. On the other hand, frameshift variations or deletions may altogether abolish the transporter and cause an insufficient therapeutic response.[10,28] In a recent study on nine patients with BTBGD, nearly half of the patients had an average cognition (56%), mild-severe delay (44%) and poor visual-motor integration (55%).[28] Understanding and mathematical problem solving were the least affected domains.[28] Long-term data on the surviving patients is limited and shall evolve with more recognition and survival.

## Conclusion

BTBGD is a pan-ethnic, underdiagnosed, treatable neurometabolic disorder. It should be suspected in all infants and children with unexplained encephalopathy and bilateral basal ganglia lesions on neuroimaging, with or without lactic acidosis. High dose biotin and thiamine should be administered to all these patients during the emergency care itself to optimize the outcomes and to identify the misdiagnosed cases. Genetic testing confirms the diagnosis and treatment is life-long. The prognosis depends on the time from diagnosis to the time of vitamin supplementation. The genotype-phenotype correlations are not clear yet, but the early infantile phenotype portends a poorer prognosis.

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### Conflicts of interest

There are no conflicts of interest.

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