Early treatment of biotin–thiamine–responsive basal ganglia disease improves the prognosis

Dorota Wesól-Kucharska a, Milena Greczan a, Magdalena Kaczor a, Magdalena Pajdowska b, Dorota Piektowska-Abramczuk c, Elżbieta Ciara c, Paulina Halat-Wolska c, Paweł Kowalski c, Elżbieta Jurkiewicz a, Dariusz Rokicki a, bla-Kucharska, Milena Greczan, Magdalena Kaczor, Magdalena Pajdowska, Dorota Piektowska-Abramczuk, Elżbieta Ciara, Paulina Halat-Wolska, Paweł Kowalski, Elżbieta Jurkiewicz, Dariusz Rokicki

a Department of Pediatrics, Nutrition and Metabolic Diseases, The Children's Memorial Health Institute, Warsaw, Poland
b Department of Biochemistry, Radioimmunology and Experimental Medicine, The Children's Memorial Health Institute, Warsaw, Poland
c Department of Medical Genetics, The Children's Memorial Health Institute, Poland
d Department of Diagnostic Imaging, The Children's Memorial Health Institute, Warsaw, Poland

ABSTRACT

Background: Biotin-thiamine-responsive basal ganglia disease (BTBGD) is an autosomal recessive neurometabolic disorder associated with pathogenic variants in SLC19A3 gene. The clinical picture includes symptoms of subacute encephalopathy (e.g. confusion, dysphagia, dystarthis, and seizures), which respond very well to early treatment with thiamine and biotin.

Method: A retrospective review of clinical characteristics, magnetic resonance imaging and molecular findings in 3 patients with BTBGD.

Results: The first symptoms in all patients occurred at 12–24 months of age and they had subacute encephalopathy, ataxia and dystonia. The baseline magnetic resonance imaging demonstrated abnormal signal intensity in the basal ganglia with atrophy and necrosis of the basal ganglia during follow-up in two patients. One patient was diagnosed and the treatment was initiated after a long period from symptoms onset and he is currently severely affected, with dystonia, quadriapsis and seizures. The other two patients were diagnosed early in life and are currently stable on treatment, without the clinical symptoms. Genetic testing demonstrated pathogenic variants in SLC19A3 gene.

Conclusion: To avoid diagnostic errors and delayed or incorrect treatment, BTBGD must be recognized early. Adequate prompt treatment gives the chance of significant clinical improvement. Unexplained encephalopathy and MRI abnormalities including bilateral abnormal signal in the basal ganglia should alert the clinician to consider BTBGD in the differential, and the treatment with biotin and thiamine should be introduced immediately.

1. Background

Biotin–thiamine–responsive basal ganglia disease (BTBGD) (#607483) is an autosomal recessive neurometabolic disorder associated with pathogenic variant in SLC19A3 gene (*606152), encoding a thiamine-transporter 2 (hThTr2). BTBGD is also referred to as thiamine responsive basal ganglia disease (BTBGD). Thiamine (or vitamin B1) is a crucial cofactor involved in multiple cellular metabolic processes, like energy metabolism as well as synthesis of nucleic acids, antioxidants, lipids, and neurotransmitters. As humans cannot synthesize thiamine, it is an essential nutrient. Free thiamine and thiamine monophosphate (TMP) are absorbed in the small intestine by two specific transporters: thiamine transporter-1 (hThTr1, encoded by SLC19A2 gene) and thiamine transporter-2 (hThTr2 encoded by SLC19A3 gene). Their specific location in the blood–brain barrier supports transport of thiamine into the central nervous system (CNS) [1,2,3]. Currently, four genetic defects (SLC19A2, SLC19A3, SLC25A19, and TPK1 genes) associated with impairment of thiamine transport and metabolism of thiamine have been described [1,2,4].

Pathogenic variants in SLC19A3 gene lead to 3 clinical forms with

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different age of onset: 1) early-infantile Leigh-like syndrome/atypical infantile spasms; 2) classical childhood BTBGD; and 3) adult Wernicke’s-like encephalopathy, with BTBGD being the most common [5,6,7]. The BTBGD occurs most frequently in children aged 3 years. The clinical picture includes signs and symptoms of subacute encephalopathy, such as confusion, dysphagia, dystarthis, seizures, external ophthalmoplegia, and generalized stiffness following a history of febrile illness. Without early and proper treatment, the disease progresses to severe quadriaparesis, rigidity, dystonia, coma, and death [8,9].

Poor prognostic factors include early onset of the disease, missed or delayed diagnosis, systemic involvement including respiratory failure and rhabdomyolysis, and severe neurological deficit or radiological findings at diagnosis and treatment initiation [5,10,11].

There are no typical biochemical criteria of BTBGD, except for low free-thiamine concentration in the cerebrospinal fluid (CSF). Elevated blood/CSF lactate concentrations and abnormal excretion of organic acids in urine are not usually present, except high excretion of alpha-ketoglutaric acid and/or lactate in urine in some patients [1]. Neuro-radiological findings include bilateral abnormal signal intensity in the basal ganglia with swelling during acute crises, specifically in the central part of the caudate heads and in part of the putamen. Abnormal signal intensity in the thalamus, globi pallidi, lesions in cerebral hemispheres cortex and brain atrophy are also observed [9,12,13].

Regardless of phenotype BTBGD responds well to the administration of high doses of thiamin (5–10 mg/kg/day) and thiamine (10–40 mg/kg/day, between 300 and 900 mg/day) and the symptoms reappear within few month after discontinuation [5,11,14].

2. Methods

We retrospectively reviewed the medical records of three patients with BTBGD including clinical data, magnetic resonance imaging and molecular findings.

Genetic tests were performed with use of next-generation sequencing (NGS). Whole-exome sequencing (WES) in patient 1 and multigene panel in the other two cases (home-made 1000 genes in patient 2, TruSight One in patient 3) was performed as previously described [15,16]. NM_025243.3 and NP_079519.1 were used as reference cDNA and protein sequence for wild-type SLC19A3 gene, respectively.

3. Results

Table 1 summarizes the clinical, biochemical and genetic data of patients with SLC19A3 defects.

| Patients | 1 | 2 | 3 |
|----------|---|---|---|
| SLC19A3  |
| molecular variant and zygosity status | c.68G > T, p. (Gly23Val) homozygous | c.74dupT, p. (Ser25Leufs*19) both heterozygous | c.337 T > C, p. (Tyr113His) both heterozygous |
| Sex      | Male | Male | Female |
| Onset age | 12 m | 24 m | 17 m |
| Current age | 10 y 1 m | 5 y 2 m | 6 y 1 m |
| Psychomotor development until the first symptoms | Mild hypotonia | Hypotonia, decreased emotional contact | Mild delayed speech development |
| First symptoms and neurological condition at diagnosis | (12 m), extrapyramidal features, dystonia, tremor (14 m), seizures, dysphagia and feeding problems (15 m) | (14 m) Recurrent mild gait instability during infected (24 m), falls, stopped walking, ataxia, ptosis (32 m) | Decreased alertness and gait instability, stopped walking, hypotonia, weakness, dystonia, tremor |
| Triggering factor | Plasma lactate concentration (N: 0.7–2.1 mmol/L) 2.3 | CSF lactate concentration (N: 1.1–1.8 mmol/L) 1.7 | nd |
| Plasma pyruvate concentration (N: 0.05–0.1 mmol/L) 0.11 | 0.07 | 0.12–0.24 |
| Lactate/ pyruvate ratio (N: 20) 23 | 19.6 | 41–26 |
| Alanine (N: 167–439 μmol/L) 216 | 429 | 396 |
| Organic acid analysis in urine | Normal | Mild excretion – 2-methyl 3-hydroxybutyric acid | High excretion of lactate |
| Baseline brain MRI/ patient’s age | Swelling of the basal ganglia with cystic degeneration in both lenticular nuclei, bilateral lesions in the crus cerebri, cortex and gray-white matter junction / 12 m | Hyperintense signal in both putamina, heads of the caudate nuclei, multiple punctate and linear lesions in cerebral hemispheres cortex / 2 y 6 m | Swelling of all basal ganglia and medial nuclei in thalamus, multiple cortical-subcortical changes in cerebral hemispheres, one focal lesion in the medulla / 17 m |
| Nijmegen score | 8 | 7 | 7 |
| Treatment initiation | 22 m | 2 y 6 m | 17 m |
| Daily dose of thiamine | 200–500 mg | 300 mg | 300 mg |
| Dose of thiamine | 5–100 mg | 20–40 mg | 20–40 mg |
| Currently neurological examination/ time of follow up | Clinical stable, tetraparesis and severe extrapyramidal syndrome with dystonia, seizure | Normal / 3 y 4 m | Normal / 4 y 6 m |

(continued on next page)
and biotin (5 mg daily) was started (and after the age of 5 the doses were increased to 500 mg and 100 mg, respectively). No clinical improvement was observed during the vitamin supplementation, currently the course of the disease is stable, epileptic seizures are completely controlled with antiepileptic drugs and ketogenic diet. MRI performed a few months after starting the treatment, showed generalized cortical and subcortical atrophy, the signal of thalami and cerebral cortex normalized, abnormal signal of the atrophic basal ganglia decreased, and the size of cystic lesions diminished. Now, he is 10 years old lying boy, with tetraparesis, he has emotional contact with his parents, and requires feeding by PEG.

**Patient 2.** The boy was born from the first pregnancy, at 39 weeks of gestation, and with a good clinical condition (3550 g; 10 Apgar score). His mother had a stroke of unknown etiology in early childhood and now she is healthy, without neurological deficits. The boy’s motor development up to the age of 2 was normal, but he presented mild delay in speech development (he spoke only a few words). From 2 years of age, the boy demonstrated recurrent balance disorders and mild gait instability during infections, which gradually disappeared. At 2.5 years of age he had an episode of subacute encephalopathy not related to the infection. The boy was falling over, stopped walking, and presented ataxia, ptosis and irritability.

Blood and CSF lactate concentrations were at the upper normal range, biotinidase deficiency was excluded, alanine concentrations were

| Patients | 1 | 2 | 3 |
|----------|---|---|---|
| Follow-up MRI / patient’s age | Control with anticonvulsant treatment and ketogenic diet/ 9 y | 1 m | Generalized cortical and subcortical atrophy, the signal of thalami and cerebral cortex normalized, decreased abnormal signal of the atrophic basal ganglia, diminished the size of cystic lesions / 3 y |
| | In the basal ganglia image bilateral striatal necrosis, the other changes regressed/ 24 m | | |

CSF- cerebrospinal fluid; m – month; N – normal; nd – no data; y – year; * according RefSeq: NM_025243.3; NP_079519.1

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**Fig. 1.** Patient 2 at the age of 2.5 years. MR brain imaging. Axial FLAIR (a, b, c), diffusion weighted image (DWI) (d), apparent diffusion coefficient (ADC) (e), and T2-weighted (f, g) images. Multiple, punctate and linear lesions are visible in both cerebral hemispheres cortex (arrows on pictures a, b, c). Some of them are hyperintense on DWI (arrow on d) and hypointense on ADC map indicated restricted diffusion (arrow on picture e). Hyperintense signal in both putamina (arrows on picture f) and heads of the caudate nuclei is seen on pictures b, c, g. Additional asymmetric involvement of the caudate nuclei (arrow on picture g).
normal, excretion of organic acids analysis in urine showed nonspecific changes (excretion of 2-methyl 3-hydroxybutyric acid). The brain MRI revealed changes in both putamina, heads of the caudate nuclei, multiple punctate and linear lesions in cerebral hemispheres cortex (Fig. 1). Metabolic disease was suspected and administration of “mitochondrial cocktail” containing thiamine (300 mg daily), biotin (20 mg daily), arginine, and folinic acid was introduced. The boy’s condition improved significantly in a few days - he started walking alone, irritation, ataxia and ptosis retreated. After establishing of the diagnosis of BTGBD confirmed by identification of two pathogenic variants in SLC19A3 gene (c.74dupT and c.980-14A > G by multigene panel sequencing) the treatment with the supplement cocktail was discontinued, leaving thiamine (300 mg) and biotin (40 mg). The control brain MRI (after 10 months of treatment) revealed complete regression of the previously described changes (Fig. 2).

Parents are carriers of one of the pathogenic variants in the SLC19A3 gene, which is present in their son, the disease was excluded in younger asymptomatic sisters of the boy.

The boy is 5 years old now, his neurological examination is normal, his speech development is still slightly delayed and he remains under speech therapy.

**Patient 3.** The girl was born from a second pregnancy, at a time (39 weeks of pregnancy) by Caesarean section due to the lack of progress of delivery, with a good clinical condition (3100 g, 10 Apgar score). Her psychomotor development was normal. At 17 months of age, a few days after infection with a subfebrile condition and rash, decreased alertness, gait instability and dystonic movements of the limbs occurred. She stopped getting up and walking on her own. Blood lactate and pyruvate concentrations were elevated, particularly after glucose supply, lactates were also present in the urine. Serum alanine concentrations and biotinidase activity were normal. MRI of the brain showed swelling of all basal ganglia and medial nuclei in thalamus, multiple cortical-subcortical changes in cerebral hemispheres and one focal lesion in the medulla.

![Fig. 2. Patient 2. Follow-up MR examination at the age of 3.5 years. Axial FLAIR (a, b) and T2-weighted (c, d) images revealed complete regression.](image-url)
Pyruvate dehydrogenase deficiency (PDH) was suspected and thiamine (300 mg daily - about 30 mg/kg/d) and the treatment with carbohydrate restricted diet were included. The girl’s condition improved significantly in a few days, the dystonia and tremors subsided, she began to get up on her own. MRI performed six months after starting the treatment showed bilateral striatal necrosis but the other changes regressed. The girl’s condition remained good; the neurological examination was normal. Lactate and pyruvate concentrations normalized. Negative results for PDH were obtained. Due to BTBGD suspicious, biotin (20 mg daily) was added to the treatment. Parents did not believe in the disease and discontinued treatment, but after a few weeks, during upper respiratory tract infection, limb dystonia reappeared. Treatment was reinitiated and complete remission of the symptoms was achieved. Confirmation of BTBGD disease was obtained - two pathogenic variants (c.337 T > C and c.958G > A) in the SLC19A3 gene were found by multigene panel sequencing. The first variant is known, pathogenic, the second variant - is a new variant, not described before, according to ten prediction algorithms, the variant is considered probably pathogenic. Parents are carriers of one of the pathogenic variants in the SLC19A3 gene, which is present in their daughter, the disease was excluded in two asymptomatic sisters of the girl.

The girl is currently 6 years old, develops properly with no symptoms.

4. Discussion

We present three patients with ThTR2 deficiency with acute encephalopathic episodes. Their condition improved and their symptoms relieved when the thiamine administration was started, with the exception of the patient treated at late stage of the disease. The global prevalence of BTBGD is about 1 of 215,000 to 1,000,000 live births. More than 50% of 135 cases reported until now come from Saudi population. Among 41 different SLC19A3 pathogenic variants the c.980-14A > G variant is the most common in the European population [1,10,18,19,20].

Patients with BTBGD usually show normal psychomotor development until the first episode of encephalopathy. The disease occurs at the median age of 3 years (range 1 month to 34 years), and in the majority of cases is triggered by infections, trauma, profuse exercise, and vaccination. In about 40% of cases the final diagnosis is preceded by more than one encephalopathy episode. The signs and symptoms in presented patients was similar to the known classical clinical picture of BTBGD [5,6,18,21].

There is no specific and sensitive biochemical marker for BTBGD, but some abnormal biochemical tests are seen more frequently in younger patients [7,12,22]. In the presented cases, elevated serum lactate was found in one patient, while in others it remained on the upper limit of normal. After the inclusion of thiamine, lactate concentration normalized.

Due to profound decrease of free-thiamine in the CSF and fibroblasts in SLC19A3-mutated patients, its CSF concentration can be used as a biomarker for diagnosis and treatment monitoring. Thiamine concentration in the CSF normalizes after oral supplementation probably through an alternative transport system [1,3,6,18]. Contrary to thiamine secondary deficiency, total blood thiamine concentrations are normal [18].

The biochemical abnormalities detected in BTBGD including mildly elevated lactate in blood and CSF, high excretion of α-ketoglutarate, and increased concentrations of leucine and isoleucine, could result from the decreased activity of thiamine-dependent mitochondrial enzymes [22]. The majority of patients have no abnormalities in respiratory pyruvate dehydrogenase activity in fibroblasts and mitochondrial substrate oxidation rates and chain complex activities [3]. However, the presence of a pyruvate peak on brain magnetic resonance spectroscopy (MRS) during an episode of acute encephalopathy was described [20]. It is known that normal cells exhibit upregulated SLC19A3 expression under stress, but this adaptive stress induced upregulation of gene expression is lost in BTBGD patients. Therefore, there is an insufficient supply of thiamine through the blood-brain barrier and symptoms of deficiency of thiamine-dependent enzymes - including PDH - occur [20]. Very often patients with finally diagnosed BTBGD were suspected of mitochondrial disease [18,23]. Our patients were diagnosed with the Nijmegen score (mitochondrial disease score) presumptively (patients 2 and 3) and defined mitochondrial disease (patient 1) [15].

The MRI findings consists of bilateral necrosis in the basal ganglia with severe edema during the acute crisis, and volume loss and necrotic changes during long term observation. The most common parts of the basal ganglia involved are the heads of caudate nuclei, putamen, and globi pallidi [6,23]. Progressive brain atrophy is a relatively common finding [24]. Several metabolic diseases, e.g. glutaric aciduria type 1, methylmalonic acidemia, and 3-methylglutaconic aciduria, may also manifest as acute or subacute necrotizing encephalopathies involving the basal ganglia. The differential diagnosis of BTBGD also includes mitochondrial disorders, in particular Leigh syndrome and PDHC deficiency [21,25]. It is also possible, that due to extensive brain changes the differentiation with ADEM (acute disseminated encephalomyelitis) is required, especially when symptoms are preceded by infection [26].

The first symptom of the BTBGD is subacute encephalopathy. However, routinely in its diagnosis, the concentration of thiamine in CSF is not determined, and there is no other specific biomarker. Therefore, we suggest that in the case of specific changes in MRI in children with subacute encephalopathy, immediately initiate treatment of biotin and thiamine and perform rapid molecular diagnostics that will take into account the above-mentioned diseases, especially BTBGD.

The combination of biotin and thiamine is effective in preventing the recurrence of the encephalopathy crisis in BTBGD and even leads to resolution of clinical symptoms and changes in additional tests (biochemical and MRI) when appropriate treatment is started quickly. No further episodes of encephalopathy, dystonia, or other neurological disturbances were noted after vitamin supplementation, half of treated patients had no disability at all, and neurological examination was normal [18]. However, the symptoms reappear within a few months if the treatment is discontinued – as we observed in our patient 3 [5,14].

Biotin and thiamine transporters in the basal ganglia are closely associated and they act synergistically. The first patient showed a good response to biotin alone [25]. Further observations showed that some patients did not improve until thiamine was added to the treatment [9,21,27]. Furthermore, Tabarki et al. [8] reported that the combination of biotin and thiamine is not superior to thiamine alone. Indeed, one of the presented patients improved significantly after the introduction of thiamine alone.

The initiation of treatment at the onset of the first symptoms is a key to achieving significant improvement in patients with SLC19A3 pathogenic variants. Few cases reported in literature failed to initiate therapy early in the course of disease with a catastrophic outcome [28]. Poor prognostic factors mentioned above should be taken into consideration in such cases [18,28].

5. Conclusion

To avoid diagnostic errors and delayed or incorrect treatment, BTBGD must be recognized early. Adequate prompt treatment gives the chance of significant clinical improvement. Unexplained encephalopathy and MRI abnormalities including bilateral abnormal signal in the basal ganglia should alert the clinician to consider BTBGD in the differential, and the treatment with biotin and thiamine should be introduced immediately.

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Contributors statement

Dorota Wesol-Kucharska, Milena Greacz conceptualized and designed the study, collected data, carried out data analysis, drafted and revised the manuscript, and approved the final manuscript as submitted. Dariusz Rokicki conceptualized and designed the study, collected data, carried out data analysis, assisted in drafting and revising the manuscript, and approved the final manuscript as submitted. All other authors assisted in conceptualizing and designing the study, collected data or advised on the progress of data collection, assisted in drafting and revising the manuscript, and approved the final manuscript as submitted.

Declaration of Competing Interest

All authors have no conflicts of interest to disclose.

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