

Single Case – General Neurology

Biotin-Thiamine-Responsive Basal Ganglia Disease: A Case Report

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Keywords

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Abstract

Introduction: Biotin-thiamine responsive basal ganglia disease (BTBGD) is a rare autosomal recessive neurometabolic disorder characterized by diverse and variable phenotypic features, which can make diagnosis challenging. However, prompt treatment with thiamine and biotin can effectively manage the condition. Diagnosis relies on the identification of biallelic pathogenic variants in the *SLC19A3* gene. This case report describes two novel variants of uncertain significance in the *SLC19A3* gene, which may be correlated with the phenotypic manifestations of BTBGD. **Case Presentation:** Our case is a 7-month-old female infant who presented with a 3-week history of irritability, altered behavior, and refusal of newly introduced solid foods. Symptoms started with an upper respiratory tract infection, followed by lethargy, floppiness, and abnormal movements. The patient was admitted to the pediatric ward with a broad differential diagnosis. Extensive laboratory evaluations revealed lactic acidosis. MRI brain showed symmetric restricted diffusion affecting the bilateral basal ganglia, thalami, and cortical regions. Whole genome sequencing identified biallelic variants of the *SLC19A3*: a c.1364T>G p.Met455Arg missense variant in the maternal allele and a 2.3 kb deletion of intron 3 of the paternal allele. Both variants were identified as variants of uncertain significance. However, given the clinical picture, MRI brain findings, resolution of symptoms with empiric biotin and thiamine supplementation, and biallelic *SLC19A3* variants of unknown significance, the patient most likely suffers from BTBGD. Patient continues to show sustained developmental progress on biotin and thiamine supplementation. **Conclusion:** This case highlights the fact that genetic testing remains a vital but improvable tool for the diagnosis of BTBGD. As of yet, genetic testing and diagnosis of BTBGD continues to be limited by the knowledge of which *SLC19A3* variants are established to be pathogenic variants. Thus, further research is required to study other *SLC19A3* variants of unknown significance to further improve genetic testing and diagnosis of BTBGD in the future.

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Introduction

Biotin-Thiamine responsive basal ganglia disease (BTBGD) is a rare disease with variable clinical presentation, which can make it difficult to diagnose. In this report, we discuss clinical presentation, diagnosis, and empiric management of BTBGD in a 7-month-old female infant.

Case Presentation

A 7-month-old female infant presented with a 3-week history of irritability, altered behavior, decreased sleep duration, and reduced oral intake. Initial symptoms began with refusal of newly introduced solid foods, followed by decreased breastfeeding frequency. The mother reported a concurrent decline in the patient's interaction, smiling, and eye contact, accompanied by a 3-week history of head lag. One week prior to presentation, the patient developed symptoms of an upper respiratory tract infection, including a dry cough, rhinorrhea, and congestion, without reported fever, nausea, vomiting, chills, or rash. The patient's initial symptoms progressively worsened, particularly 4 days prior to presentation, characterized by increased lethargy, floppiness, and decreased interactions. The mother also noted abnormal movements when the patient was placed in an upright position from supine, described as brief episodes of loss of balance. One day prior to admission, the patient was evaluated by her primary care physician, who noted a 1-pound weight loss, decreased urine output, and prescribed cefdinir (Omnicef) for her respiratory symptoms. Subsequently, the patient developed watery diarrhea without changes in stool color or odor. The patient's medical history is notable for normal well-child examinations at 2, 4, and 6 months, with no reported trauma, canned food ingestion, travel, or accidental medication ingestion. No relevant family history noted on initial evaluation.

Upon physical examination, the patient presents as irritable and unwell. Vital signs are within normal limits for her age. Ocular examination reveals equal, round, and reactive pupils. The nose is congested, and mucous membranes are dry, indicating dehydration. However, there are no signs of respiratory distress. Lung auscultation reveals good air entry bilaterally, with transmitted upper airway sounds heard in both lung fields. Cardiac examination reveals a regular rate and rhythm, with no murmurs, and normal pulses and capillary refill. Abdominal examination is unremarkable, with no tenderness, distension, masses, or hepatosplenomegaly. The patient moves all four limbs spontaneously, with no evidence of truncal weakness. However, she exhibits a moderate head lag when pulled to a sitting position from supine, indicating hypotonia. Neurological examination reveals 2+ patellar reflexes bilaterally, with no ankle clonus. There are no skin rashes or other cutaneous lesions observed.

Abdomen and chest X-ray done in an outside hospital were unremarkable. Initial Laboratory investigations in the ED revealed the following findings: white blood cell count, $9.5 \times 10^9/L$ with 17% neutrophils, 73% lymphocytes, and 9% monocytes; hemoglobin level, 11.9 g/dL; platelet count, $451 \times 10^9/L$; sodium level, 141 mmol/L; potassium level, 4.9 mmol/L; chloride level, 106 mmol/L; bicarbonate level, 11 mmol/L; blood urea nitrogen level, 6 mg/dL; creatinine level, 0.28 mg/dL; calcium level, 10.8 mg/dL; albumin level, 4.8 g/dL; aspartate aminotransferase, 70 U/L; alanine aminotransferase, 26 U/L; alkaline phosphatase, 128 U/L; bilirubin total, 0.2 mg/dL; lactic acid, 5.8 mmol/L; procalcitonin, 0.08 ng/mL.

The patient received two boluses of intravenous fluids (IVFs) and was subsequently admitted to the pediatric ward for further management. Upon admission, the differential diagnosis for the patient's hypotonia and abnormal ocular movements was broad, encompassing inborn

errors of metabolism, endocrine disorders, primary neuromuscular conditions, and central nervous system infections. Consequently, a comprehensive laboratory evaluation was initiated, yielding normal results for creatine kinase, aldolase, thyroid function tests, urinalysis, culture, uric acid, C-reactive protein, and ammonia levels. Additionally, a respiratory infectious disease panel revealed a concomitant upper respiratory viral infection with coronavirus OC43 and parainfluenza 3. The patient's diarrhea was likely a consequence of antibiotic treatment, as it commenced following the administration of Omnicef. The patient's anion gap metabolic acidosis and elevated lactic acid levels prompted consideration of two primary differential diagnoses: first, dehydration secondary to decreased oral intake and viral upper respiratory infection, and second, a potential metabolic process. Consultation with pediatric neurology was sought early in the hospital course.

On the third day of admission, the patient exhibited a notable neurological episode upon waking, characterized by a staring spell and lack of tracking. This was accompanied by crying and an irregular breathing pattern, lasting approximately 30–60 s. Subsequently, the patient resumed tracking. An urgent magnetic resonance imaging (MRI) scan of the brain (shown in Fig. 1) revealed symmetric restricted diffusion affecting the bilateral basal ganglia, thalami, and cortical regions of the bilateral cerebral hemispheres, with predominant involvement of the mid and posterior regions and relative sparing of the frontal regions. Additionally, generalized volume loss was observed in the cerebral hemispheres. Radiological interpretation suggested evolving cytotoxic/ischemic changes, with a high likelihood of an underlying metabolic or genetic disorder, particularly mitochondrial disorders. Continuous electroencephalography monitoring overnight did not detect any seizure activity but showed mild encephalopathy with bi-posterior slowing. Furthermore, magnetic resonance spectroscopy revealed an abnormal signal in the right thalamus, with elevated choline and reduced N-acetylaspartate levels (shown in Fig. 2), consistent with tissue abnormality, although the pattern was nonspecific.

A lumbar puncture was performed, and cerebrospinal fluid (CSF) analysis revealed an abnormal profile, characterized by pleocytosis (elevated nucleated cell count), elevated lactic acid, and elevated protein levels. Further CSF evaluation, including amino acid analysis, pyruvate levels, complete blood cell counts, and a comprehensive meningoencephalitis panel, yielded normal results. Additional laboratory tests were conducted, including serum amino acids, acylcarnitine, carnitine, lactate, pyruvate, ammonia, fatty acids, lipid profile, basic metabolic panel, magnesium, and phosphorus levels, all of which were within normal limits. Furthermore, urine organic acid and acylglycine levels were also normal, ruling out various metabolic and genetic disorders.

During her hospitalization, the patient displayed persistent and pronounced hypertonia of the extremities, accompanied by significant irritability. To manage these symptoms, she was initiated on scheduled regimen of clonidine and as-needed doses of diazepam (Valium), which has resulted in effective mitigation of her hypertonia and irritability. Nasogastric tube feeds were initiated due to the patient's lack of interest and concern for oral feeding safety during episodes of irritability. Furthermore, the patient required escalation of respiratory support and was placed on high-flow nasal cannula therapy on the fifth day of admission for a duration of 48 h, due to the development of respiratory distress characterized by increased work of breathing, head bobbing, and intermittent grunting. Throughout her hospitalization, the patient exhibited persistent metabolic acidosis, characterized by elevated lactate levels, with a peak lactate level of 9 mmol/L on the fifth day of admission. Initial management involved administration of sodium bicarbonate (50 meq/L) in her IVF regimen, followed by transition to citric acid-sodium citrate 500-334 mg/5 mL oral solution (3 mL 4 times daily). The acidosis eventually resolved.

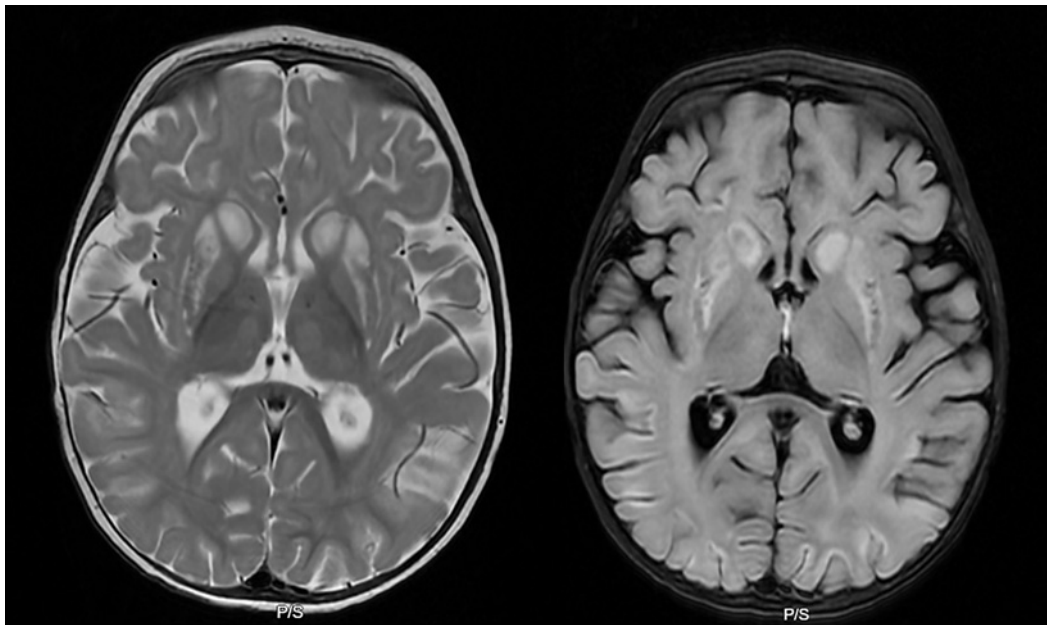


Fig. 1. MRI brain without contrast, axial section, showing symmetric restricted diffusion of the bilateral basal ganglia and thalami. There is also more subtle symmetric restricted diffusion of the cortex of the bilateral cerebral hemispheres predominantly affecting the mid and posterior regions with some sparing of the frontal regions. There is generalized volume loss of cerebral hemispheres.

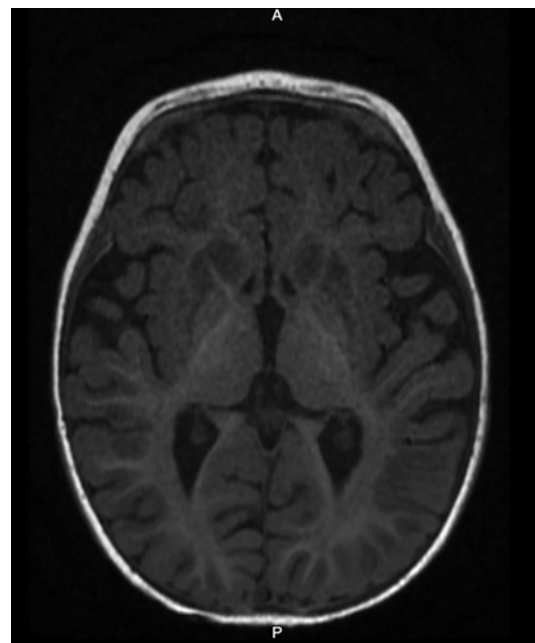


Fig. 2. MRI brain with contrast: multi-voxel spectroscopy with echo time of 144 ms preformed on right cerebral hemisphere, with most voxel placed in the region of right thalamus (in an area which has normal signal on conventional sequence. Two repetition of spectroscopy were performed) Spectroscopy was abnormal with elevated choline peak and reduced NAA, a nonspecific finding, but consistent with tissue abnormality. Overall spectroscopy of the right thalamus is abnormal, in an area, without distinct signal abnormality on conventional sequences. NAA, N-acetylaspartate.

Consultation with the biomedical genetics service was obtained, and rapid genome sequencing was recommended, which was subsequently undertaken. The patient exhibited general clinical improvement throughout her hospitalization, prompting discontinuation of acute care and transition to inpatient rehabilitation for ongoing physical and oral motor therapy, following a 2-week hospital stay.

Following discharge, whole genome sequencing revealed two variants in the *SLC19A3* gene, associated with a diagnosis of biotin-thiamine responsive basal ganglia disease. Consequently, the patient was started on empirical biotin and thiamine therapy, to which she demonstrated a positive clinical response. Based on the genetic testing results and clinical presentation, BTBGD is the current working diagnosis, pending confirmatory clinical evaluation. Research options are being explored to further confirm the diagnosis. In the interim, the patient continues to show improvement on biotin and thiamine supplementation, with sustained developmental progress and no regression since initiating treatment.

Discussion

With only 135 prior documented cases as of 2019, BTBGD can be an incredibly difficult disease to diagnose given the rarity and the subsequent lack of awareness of the disease [1]. The presentation of BTBGD itself is not necessarily uniform in nature. BTBGD has been documented with three different types of distinct presentations: classic, Leigh-like, and Wernicke-like. Patients with the classic presentation of BTBGD often present between the ages of 3–10 years old with a slew of symptoms including ataxia, dystonia, cogwheel rigidity, external ophthalmoplegia, superficial facial palsy, seizure, confusion, encephalopathy [2]. The Leigh-like syndrome of BTBGD often presents with vomiting, feeding problems, encephalopathy, and severe lactic acidosis within the first 3 months of the patient's life [3]. Finally, the Wernicke-like form of BTBGD is one that typically appears in adults during their second decade of life with symptoms of ataxia, ophthalmoplegia, nystagmus, diplopia, and status epilepticus [4]. As previously described, our patient's presentation most accurately matches that of the Leigh-like syndrome presentation of BTBGD. Interestingly, our patient's BTBGD arose following an infection with coronavirus OC43 and parainfluenza 3. Febrile infection along with mild trauma and stress has been documented in the literature as triggers for the onset of BTBGD [5]. The patient's lactic acidosis at admission was likely precipitated by the infection and subsequent dehydration. However, the lactic acidosis persisted despite adequate IVF resuscitation, and only resolved with the initiation of sodium bicarbonate therapy and subsequent addition of Bicitra. Furthermore, the infantile presentation and characteristic magnetic resonance imaging (MRI) findings are more consistent with a diagnosis of Leigh-like syndrome associated with BTBGD [3].

Given BTBGD's presentation with relatively nonspecific neurological findings, the differential is often quite broad including various neurological, vascular, infectious, mitochondrial, metabolic, and toxic disorders. Even after narrowing the differential down to metabolic disorders affecting the basal ganglia, several other disorders remain in consideration. Deficiency in thiamine pyrophosphokinase, an enzyme required to convert thiamine into a usable form for the body, is another metabolic disorder that can lead to thiamine deficiency-related basal ganglia lesions [6]. Guanidinoacetate methyltransferase deficiency prevents creatine synthesis leading to creatine deficiency and accumulation of its precursor molecule resulting in changes to the basal ganglia [7]. Patients with organic acid disorders including isolated methylmalonic acidemia, maple syrup urine disease, and propionic acidemia have a deficiency in various enzymes required to break down proteins leading to the toxic accumulation of these proteins and subsequent basal ganglia injury [8–10]. Several disorders that lead to the accumulation of lipids known as GM1 and GM2 gangliosidoses, most well-known of which is Tay-Sachs, can also lead to basal ganglia lesions [11].

In the process of diagnosing BTBGD, two commonly ordered diagnostics include lumbar puncture with CSF analysis and an MRI brain. Whilst these diagnostics do not have findings that are necessarily specific or diagnostic for BTBGD, they can still present with common

findings that can help guide providers closer toward the diagnosis. Of note, the literature has demonstrated that the CSF of BTBGD often contains elevated levels of lactic acid and decreased levels of free-thiamine [12, 13]. We did not test for levels of free-thiamine but our patient did similarly have elevated levels of lactic acid in addition to elevated nucleated cells and protein in her CSF. Furthermore, MRI brain frequently demonstrates progressive atrophy as well as lesions to the basal ganglia and to the thalamus [3]. Of the aforementioned findings typically found in BTBGD patients, our patient did demonstrate tissue abnormalities in the right thalamus.

Ultimately, BTBGD requires genetics testing for a diagnosis. After all, the condition is caused by a defect to the *SLC19A3* gene. The *SLC19A3* gene is responsible for the production of thiamine transporters within the duodenum [14]. Thus, defects in this particular gene lead to problems with thiamine metabolism which causes the symptomatology of BTBGD. The diagnosis of a genetic disorder requires the identification of biallelic pathogenic variants of the affected gene; so simply put, the diagnosis of BTBGD requires the identification of two mutated copies of the *SLC19A3* gene that have been previously determined to cause the disease [5]. In the case of our patient, genetic testing identified biallelic variants of the *SLC19A3*: a c.1364T>G p.Met455Arg missense variant which describes a singular point of error in the DNA of the maternal allele and a 2.3 kb deletion of intron 3 which entails a deletion of an entire section of the paternal allele. Unfortunately, both of these variants are identified as variants of uncertain significance as they have never been previously linked with BTBGD. As such, the patient does not meet the diagnostic criteria to establish the diagnosis of BTBGD.

Despite inconclusive genetic testing, the patient was treated with the presumed diagnosis of BTBGD. BTBGD patients receive life-long supplementation of biotin and thiamine leading to rapid resolution of symptoms within days of initiating treatment [5]. The continuation of this treatment is necessary as lapses in treatment can lead to the re-appearance of symptoms [15].

Additionally, cases in the literature have documented the fatal consequences of failing to initiate treatment, further underscoring the importance of timely treatment and diagnosis of BTBGD [16]. However, there is newer data that suggest that biotin supplementation may not be necessary in the treatment of BTBGD [17]. Our patient was initiated on biotin and thiamine supplementation during hospitalization and saw large improvements in all presenting symptoms. Furthermore, as of the writing of this manuscript over a year later, the patient has continued her biotin and thiamine supplementation and remained asymptomatic.

Conclusion

This case, along with others highlighted in this study, demonstrates the highly treatable nature of BTBGD as well as the drastic consequences if not treated accurately and promptly, emphasizing the importance of timely diagnosis and treatment of this disease. It also highlights the importance of keeping a broad differential early on when patients are present with a similar clinical picture to that of BTBGD.

Genetic testing remains a vital but improvable tool for the diagnosis of BTBGD; however, this continues to be limited by the knowledge of which *SLC19A3* variants are established to be pathogenic variants. There has yet to be enough evidence to identify other *SLC19A3* variants of unknown significance (e.g., c.1364T>G p.Met455Arg missense and the 2.3 kb deletion of intron 3) as pathogenic variants. Thus, further research is required to study other *SLC19A3* variants of unknown significance to further improve genetic testing and diagnosis of BTBGD in the future.

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Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the parent/legal guardian of the patient for publication of the details of their medical case and any accompanying images. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000542886>).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.T.: obtained consent, literature review, and wrote discussion and conclusion A.A.: wrote abstract, reviewed medical records, and wrote case presentation O.Y.: wrote the introduction, adjusted parts of case presentation, discussion and wrote the final manuscript for submission S.L.P.: senior clinical responsible for patient care and reviewing and proofreading the study.

Data Availability Statement

Data supporting the findings of this case report are available from the corresponding author upon reasonable request. Patient confidentiality and ethical considerations prevent the public sharing of individual patient data.

References

- 1 Alfadhel M, Umair M, Almuzzaini B, Alsaif S, AlMohaimed SA, Almashary MA, et al. Targeted SLC19A3 gene sequencing of 3000 Saudi newborn: a pilot study toward newborn screening. *Ann Clin Transl Neurol*. 2019; 6(10):2097–103. <https://doi.org/10.1002/acn3.50898>
- 2 Pérez-Dueñas B, Serrano M, Rebollo M, Muchart J, Gargallo E, Dupuits C, et al. Reversible lactic acidosis in a newborn with thiamine transporter-2 deficiency. *Pediatrics*. 2013;131(5):e1670–5. <https://doi.org/10.1542/peds.2012-2988>

- 3 Yamada K, Miura K, Hara K, Suzuki M, Nakanishi K, Kumagai T, et al. A wide spectrum of clinical and brain MRI findings in patients with SLC19A3 mutations. *BMC Med Genet*. 2010;11:171. <https://doi.org/10.1186/1471-2350-11-171>
- 4 Kono S, Miyajima H, Yoshida K, Togawa A, Shirakawa K, Suzuki H. Mutations in a thiamine-transporter gene and Wernicke's-like encephalopathy. *N Engl J Med*. 2009;360(17):1792–4. <https://doi.org/10.1056/NEJMc0809100>
- 5 Tabarki B, Al-Hashem A, Alfadhel M. Biotin-thiamine-responsive basal ganglia disease. 1993. PubMed Published 1993. <https://www.ncbi.nlm.nih.gov/books/NBK169615/>
- 6 Xia Y, Qian T, Fei G, Cheng X, Zhao L, Sang S, et al. Low expression of thiamine pyrophosphokinase-1 contributes to brain susceptibility to thiamine deficiency. *Neuroreport*. 2024;35(15):1000–9. <https://doi.org/10.1097/WNR.0000000000002094>
- 7 Dhar SU, Scaglia F, Li FY, Smith L, Barshop BA, Eng CM, et al. Expanded clinical and molecular spectrum of guanidinoacetate methyltransferase (GAMT) deficiency. *Mol Genet Metab*. 2009;96(1):38–43. <https://doi.org/10.1016/j.ymgme.2008.10.008>
- 8 Chen T, Gao Y, Zhang S, Wang Y, Sui C, Yang L. Methylmalonic acidemia: neurodevelopment and neuroimaging. *Front Neurosci*. 2023;17:1110942. Published 2023 Jan 26. <https://doi.org/10.3389/fnins.2023.1110942>
- 9 Cheng A, Han L, Feng Y, Li H, Yao R, Wang D, et al. MRI and clinical features of maple syrup urine disease: preliminary results in 10 cases. *Diagn Interv Radiol*. 2017;23(5):398–402. <https://doi.org/10.5152/dir.2017.16466>
- 10 Marchuk H, Wang Y, Ladd ZA, Chen X, Zhang GF. Pathophysiological mechanisms of complications associated with propionic acidemia. *Pharmacol Ther*. 2023;249:108501. <https://doi.org/10.1016/j.pharmthera.2023.108501>
- 11 Regier DS, Proia RL, D'Azzo A, Tift CJ. The GM1 and GM2 gangliosidoses: natural history and progress toward therapy. *Pediatr Endocrinol Rev*. 2016;13 Suppl 1(Suppl 1):663–73.
- 12 Wang J, Wang J, Han X, Liu Z, Ma Y, Chen G, et al. Report of the largest Chinese cohort with *SLC19A3* gene defect and literature review. *Front Genet*. 2021;12:683255. Published 2021 Jul 1. <https://doi.org/10.3389/fgene.2021.683255>
- 13 Ortigoza-Escobar JD, Molero-Luis M, Arias A, Oyarzabal A, Darín N, Serrano M, et al. Free-thiamine is a potential biomarker of thiamine transporter-2 deficiency: a treatable cause of Leigh syndrome. *Brain*. 2016;139(Pt 1):31–8. <https://doi.org/10.1093/brain/awv342>
- 14 Zhao R, Goldman ID. Folate and thiamine transporters mediated by facilitative carriers (SLC19A1-3 and SLC46A1) and folate receptors. *Mol Aspects Med*. 2013;34(2–3):373–85. <https://doi.org/10.1016/j.mam.2012.07.006>
- 15 Wesół-Kucharska D, Greczan M, Kaczor M, Pajdowska M, Piekutowska-Abramczuk D, Ciara E, et al. Early treatment of biotin-thiamine-responsive basal ganglia disease improves the prognosis. *Mol Genet Metab Rep*. 2021;29:100801. Published 2021 Sep 29. <https://doi.org/10.1016/j.ymgmr.2021.100801>
- 16 Algahtani H, Ghamdi S, Shirah B, Alharbi B, Algahtani R, Bazaid A. Biotin-thiamine-responsive basal ganglia disease: catastrophic consequences of delay in diagnosis and treatment. *Neurol Res*. 2017;39(2):117–25. <https://doi.org/10.1080/01616412.2016.1263176>
- 17 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):547–52. <https://doi.org/10.1016/j.ejpn.2015.05.008>