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Child Neurology: Infantile Biotin Thiamine Responsive Basal Ganglia Disease: Case Report and Brief Review

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Abstract

Biotin thiamine responsive basal ganglia disease (BTRBGD) is an inherited autosomal recessive disorder that results from the inability of thiamine to cross the blood brain barrier.[1-3] It is considered a treatable condition if vitamin supplementation, most commonly with thiamine and biotin, is initiated early.[2] BTRBGD can present as an infantile form, classical childhood form, or adult Wernicke-like encephalopathy.[3] The infantile form is often the most severe and portends a worse prognosis with high mortality despite vitamin supplementation. We present a two-month-old who presented with irritability, opisthotonos, and abnormal eye movements who was found to have compound heterozygous variants in the SLC19A3 gene inherited in trans, including one known pathogenic intronic variant and a novel variant presumed to be pathogenic. She was therefore diagnosed with infantile BTRBGD. In this report, we discuss the differential for infantile BTRBGD, the clinical and radiologic features of BTRBGD, and describe a rapid, positive response to early vitamin supplementation in an infant with a likely pathogenic novel variant in SLC19A3.

Clinical Case

A two-month-old, ex-full term, developmentally appropriate girl presented to our institution with abnormal eye movements described as a transient forced downward gaze and exaggerated eyelid opening. Two days prior to presentation, the patient developed projectile vomiting with feeding. She remained afebrile but seemed fussier than usual. She was evaluated in an outside emergency department and discharged home. Within 24 hours, the abnormal eye movements started. Her parents described paroxysmal tonic downgaze of her eyes. This became more frequent and at the time of presentation was occurring approximately once every thirty minutes. She was admitted for evaluation of possible seizures, infantile spasms, or increased intracranial pressure, among other possible causes for new onset irritability and abnormal eye movements. On exam, her fontanelle was soft, and her neurologic exam was normal except for intermittent exaggerated eye

opening. A limited rapid MRI brain that included only a T2 sequence was unrevealing. CSF studies were normal (cell count 0/uL, glucose 53 mg/dL, protein 19 mg/dL, meningitis PCR/culture negative). Metabolic screening labs, including ammonia, acylcarnitine, plasma amino acids, L-carnitine, and urine organic acids, were normal. However, lactate was elevated at 4.9 mmol/L and remained elevated to 2.1 mmol/L on repeat testing. Twenty-four-hour video EEG monitoring showed a normal background and captured episodes of fussiness and tonic downgaze without electrographic correlate. Her spells and fussiness began to diminish spontaneously without a clear reason for resolution, but she was discharged home with a plan for further outpatient monitoring. We hypothesize that her emesis may have represented a transient viral infection contributing to fluctuating metabolic demand.

Two days later, she developed extreme irritability and recurrence of the exaggerated eye opening and paroxysmal tonic downgaze. She then developed intermittent extension and flexion of the bilateral upper extremities as well. Her parents reported regression in visual tracking, loss of social smile and head control. She was urgently readmitted to the hospital. Complete blood count illustrated a thrombocytosis of 669 x 10^9/L, but other labs, including a comprehensive metabolic panel, C-reactive protein, chromosomal microarray, urine homovanillic acid (HVA), and vanillylmandelic acid (VMA), were all normal. A peripheral venous lactate was repeated and was again elevated at 2.3 mmol/L. Forty-eight hours of video EEG remained normal including again capturing episodes of abnormal eye movements. Repeat complete brain MRI and MR spectroscopy was performed, revealing symmetric restricted diffusion in the bilateral lentiform nuclei (Figure, A) and frontal lobes along the peri-Rolandic cortex. There was also abnormal signal within the bilateral thalami (Figure, B) and cerebellar hemispheres, not present on the prior MRI. MR spectroscopy was notable for a reduction of NAA relative to other metabolites within the lentiform nucleus, suggesting neuronal injury (Figure, C). However, no lactate peak was noted, which can be suggestive of hypoxic injury or certain mitochondrial diseases, such as Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes (MELAS). No mineralization was noted on susceptibility weighted imaging, which can be seen in disorders such as Neurodegeneration with Brain Iron Accumulation (NBIA; Figure, D).

The pattern of injury was suspicious for a metabolic or mitochondrial disorder, in particular Leigh syndrome or BTRBGD; therefore, she was empirically started on high dose biotin (10mg/kg daily) and thiamine (20mg/kg daily) immediately. A GeneDx MitoXpanded panel was sent which was positive for two variants in the SLC19A3 gene, assumed to be inherited in trans. One of the variants is a previously reported (ClinVar Variation ID: 265591) intronic pathogenic variant (c.1314+1,G>A) that is known to affect RNA splicing and is hypothesized to impact SLC19A3 function.[4] The other variant (c.298 G>C, p.G100R) has not been previously reported, and thus was classified as a variant of uncertain significance, but given the patient's compound heterozygosity with a frank BTRBGD phenotype, we strongly suspect this to be a pathogenic variant. In silico analysis supports that this missense variant has a deleterious effect on protein structure and function. Trio analysis showed that the pathogenic variant (c.1314+1, G>A) was present in patient's mother, while the variant of uncertain significance (c.298 G>C) was not present in either parent, suggesting that the patient's mother was a carrier of one variant, and our patient had a de novo mutation in the opposite allele that resulted in disease.

The patient's spells and irritability resolved within 1-2 days of supplementation. As she had regressed in motor and social behavior at onset, physical therapy was started upon discharge. At follow up at 7 months of age, she was noted to have axial hypotonia, mild gross motor delay and intermittent right esotropia only, demonstrating improvement in her development after supplementation.

Discussion

Thiamine (Vitamin B1) is an important cofactor in energy metabolism.[1] Thiamine deficiency can occur from lack of intake, as in infantile beriberi, but can also be due to genetic defects in thiamine transport and metabolism.[1] There are multiple transporters in the body that allow for absorption of thiamine including SLC19A2, SLC25A19 and SLC19A3.[1] The SLC19A3 gene encodes the thiamine transporter 2, which allows thiamine to cross the blood brain barrier.[1,3] Mutations in the SLC19A3 gene cause a rare recessive metabolic condition called biotin thiamine responsive basal ganglia disease, characterized by early onset encephalopathy, bulbar dysfunction, dystonia/hypotonia, ataxia, and seizures that are often triggered by a febrile illness.[2,5] BTRBGD is considered a treatable condition if vitamin supplementation is started early. Treatment consists of a combination of high dose biotin (1-10mg/kg/day) and thiamine (10-40mg/kg/day).[5] Since biotin is not a substrate for the thiamine transporter, the role of biotin remains unclear.[6] One hypothesis is that biotin allows for accumulation of pyruvate to bypass the Krebs cycle via the biotin dependent pyruvate carboxylase enzyme.[6] Some data suggest treatment with thiamine alone is as effective as thiamine and biotin together,[5,7] though given the high safety profile of biotin, it is reasonable to empirically treat with both concurrently.

With an estimated disease prevalence of BTRBGD due to SLC19A3 mutations of 1 in 215,000[8] there are few reports of BTRBGD in the literature, especially describing cases with neonatal or infantile onset.[5, 9-15] Given its rarity, the genotype-phenotype correlation is not completely known. However, in contrast to the classical childhood- and adult-onset BTRBGD phenotypes, which often respond more effectively to supplementation,[5] infantile BTRBGD unfortunately portends a more severe phenotype with increased morbidity and mortality, despite vitamin supplementation.[5] In a cohort of patients from China, it was noted that almost all survivors with the infantile form were left with severe neurologic sequelae.[5] This outcome was echoed by another retrospective review of a cohort of seven patients, two of which had the infantile form and illustrated poor recovery despite vitamin supplementation.[14] One of those patients died within a week of initiation of supplementation and the other had spastic quadriplegia and required tracheostomy.[14] Less commonly, infantile BTRBGD patients have been described who improved with biotin and thiamine supplementation.[10,11] While not well-established, the severity of injury at initial presentation and a longer interval before treatment is thought to contribute to the historically poor outcomes. Prompt recognition, less severe clinical-radiographic presentations, and early supplementation have been noted in cases with good outcomes, including the patient reported here.[10,11] Short-term outcomes in responsive infantile onset cases have included residual MRI injuries and dystonia in some, while others have no clear sequelae; importantly long-term follow-up is lacking.

In retrospective cohorts of infantile BTRBGD, all patients presented with encephalopathy consisting of irritability, crying, and/or depressed level of consciousness.[5] They are also more

likely to have concomitant hypotonia, ophthalmoplegia, dysphagia, and lactic acidosis compared to childhood BTRBGD.[5] Due to its non-specific clinical presentation and low incidence, BTRBGD is often mistaken for other conditions, especially early in the course of the illness. Radiographic findings include symmetric T2 hyperintensities in the caudate, putamen, cortex, subcortical white matter, and/or thalami without involvement of mammillary bodies.[1] The thalami are more frequently involved in infantile onset cases.[5] The differential for this combination of clinical and radiographic findings in neonates includes hypoxic ischemic injury, metachromatic leukodystrophy, Leigh disease, periventricular leukomalacia, MELAS, and non-ketotic hyperglycinemia (NKH).[2] However, when this MRI pattern is observed, a bundled mitochondrial panel that includes mitochondrial genes encoded in both nuclear and mitochondrial DNA should be obtained. If there is very strong suspicion, targeted SLC19A3 testing could be obtained, but if negative, would not help provide alternate genetic/metabolic explanations. Crucially, these MRI brain findings have a high enough specificity for BTRBGD that, if recognized, should prompt providers to immediately initiate potentially life-saving empiric vitamin supplementation, even before a genetic diagnosis is confirmed.

Conclusion

BTRBGD is an inherited autosomal recessive disorder that affects the ability of the body to transport and utilize thiamine and can present in infancy, childhood, or adulthood. Our case is one of few that provides a critical illustration of the rapid clinical recovery that can be achieved with quick identification and therapy in an infantile disease with an otherwise severe prognosis. Though rare, clinicians should suspect BTRBGD in encephalopathic infants with symmetric basal ganglia involvement on imaging, and initiate empiric high dose thiamine and biotin prior to genetic confirmation, since immediate treatment has the potential to slow, or even reverse, disease progression and may ultimately be lifesaving.

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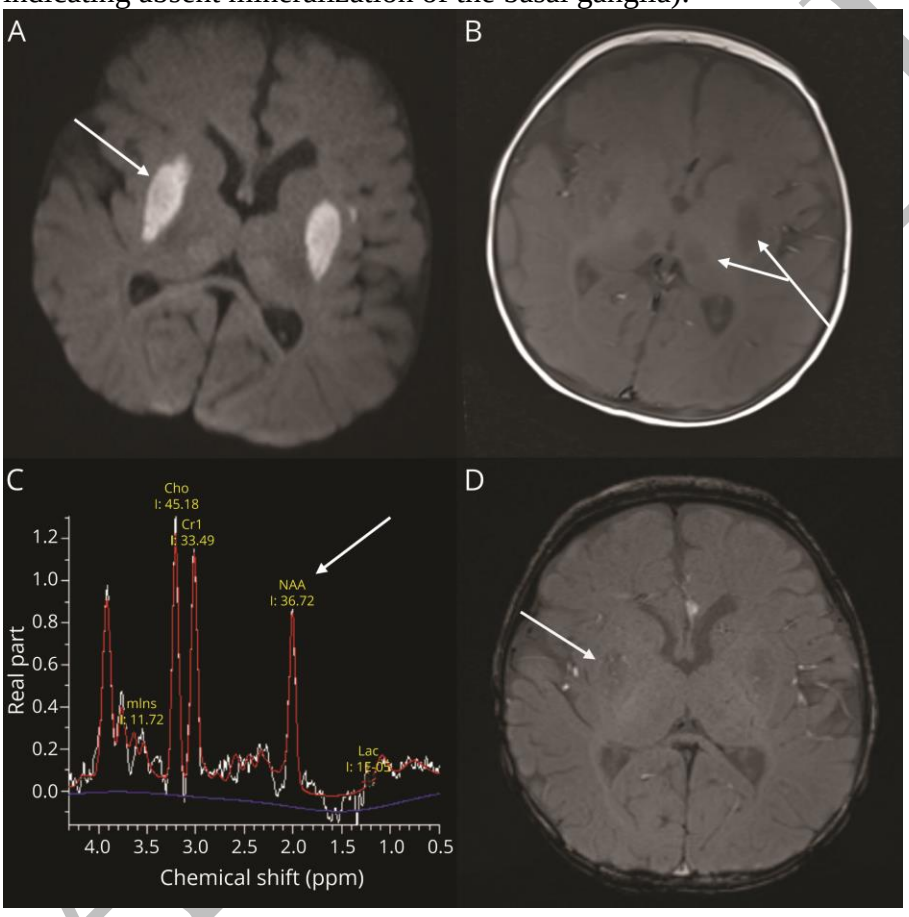
Figure 1: MRI and MR spectroscopy findings in BTRBGD

Figure 1 Caption

A) Axial DWI demonstrating diffusion restriction within the bilateral basal ganglia (arrow) and abnormal signal within the medial thalami.
B) Axial T1 demonstrating hypointensity in the bilateral basal ganglia and medial thalami (arrows).
C) MR Spectogram of the basal ganglia lesion illustrating a reduction of NAA (arrow) relative to other metabolites, suggestive of neuronal injury.
D) Axial SWI does not demonstrate abnormal mineralization or hemorrhage (arrow indicating absent mineralization of the basal ganglia).



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