Rare Case of Biotin-Thiamine-Responsive Basal Ganglia Disease Presenting in a Neonate

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Biotin-thiamine-responsive basal ganglia disease (BTBGD) has three subtypes: childhood-onset classic form, adulthood-onset Wernicke-like encephalopathy, and the much rarer early infantile form.[1] The prognosis for the former two subtypes is favorable with timely diagnosis and compliant treatment, including oral thiamine and biotin. However, the early infantile form uniformly carries a poor prognosis.[2,3] Our case highlights the clinical details of a neonate diagnosed with early infantile BTBGD, the seventh to be reported in literature and the first from India.[2,3]

A female child, second born to a nonconsanguineous Asian couple, was delivered through caesarean section due to cephalopelvic disproportion. There was no history of perinatal asphyxia. Anthropometric parameters were normal, and she had an unremarkable pedigree.

The patient first manifested clinically on day 16 of life with repeated ocular twitching and tonic posturing of the limbs. Examination revealed an irritable sensorium, appendicular hypertonia, hyperreflexia, and bilateral extensor plantars. Preliminary investigations (serum electrolytes, blood sugar, serum calcium, septic screen, blood culture, and cerebrospinal fluid analysis) returned normal. She developed resistant seizures and encephalopathy on day 19, necessitating invasive ventilation. Metabolic workup revealed mild acidosis and raised serum lactate (PH 7.2, PCO2 23 mm Hg, PO2 50 mm Hg, base excess –3 mmol/L, HCO3 14 mmol/L, lactate 4.8 mmol/L). Magnetic resonance imaging of the brain revealed restricted diffusion in bilateral putamen, thalamus, crus cerebri, and central pons, sparing the caudate nucleus; suggesting Leigh syndrome spectrum.

Our clinical suspicion included inherited neurometabolic disorder. Given the early-onset of neurological manifestations, raised lactates, and an abnormal neuroimaging, we specifically considered the possibility of mitochondrial disorders.

Thus, exome sequencing (ES) was ordered. Meanwhile, empiric daily carnitine (100 mg/kg/day), biotin (10 mg/kg/day), and thiamine (1,500 mg/day) were initiated. Over the next 7 days the child stabilized with no further seizures. Follow-up at 2 months documented age-appropriate early milestones, normal growth parameters, with persistent hypertonia and hyperreflexia.

Meanwhile, ES yielded a homozygous indel variation in *SLC19A3* (NM_025243.3; c.374_378delinsTGGTAGGTAGTATATACGCAGT; p.Ala125Valfs*21). The variant was described to be likely pathogenic as per the American College of Medical Genetics and Genomics guidelines, which confirmed the diagnosis of early infantile BTBGD in our patient. The family declined parental segregation analysis for the *SLC19A3* variant, stating financial constraints.

BTBGD was first described by Ozand et al, in 1998 in a cohort of 10 patients with the childhood-onset form.[4] The gene for the same was mapped to *SLC19A3* on chromosome-2, in 2005.[5] Later, Alfadhel et al reviewed a series of 18 cases of BTBGD, in which all patients had childhood-onset of the disease.[5] The reports so far highlighted the role of timely and simple supplementation by oral biotin and thiamine in mitigating the disease course and even ensuring a normal life in many patients. It was the landmark elucidation of four cases of BTBGD with early-infantile-onset (< 3 months) in 2010 that led to the phenotypic expansion of the disease.[2] Two additional cases of early-onset BTBGD were described recently in a case series of seven patients.[3]

The prognosis of the early infantile BTBGD has been uniformly poor. Among the six cases described, three were instituted timely supplementation; however, one still died early on day 42 of life. The other two were alive at 6 and 5 years, respectively, with serious comorbidities, being bedridden with spastic quadriparesis, dystonia, and feeding difficulties. Of the remaining three who were not given

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any supplementation, one was alive at 18 years with a similar quadriparetic course as above, while the other two expired at 12 and 9 years, respectively.

Experience of the above case reports of early infantile BTBGD and the guarded prognosis associated was outlined to the family. They were counseled to be compliant with the medicines, despite this natural history. Besides prognostication for the index patient, a precise diagnosis helped the couple understand their future reproductive options, given the possible 25% risk of recurrence for BTBGD.

Follow-up at 7 months noted good compliance for oral biotin and thiamine in the prescribed doses. However, we noted worsening of the clinical condition in the form of resurfacing of drug-resistant seizures and neuroregression. Additionally, the assessment noted feeding and swallowing difficulties, failure to thrive, evolving microcephaly, squint, and prominent dystonia. Thus, in our case, too, the response to oral biotin and thiamine was not as encouraging as otherwise noted in the childhood-onset form of BTBGD.

ES harbors a high diagnostic yield of 40 to 70% in suspected cases of inherited neurometabolic diseases.[6] Our case reiterates this strength of next-generation sequencing to truncate diagnostic odysseys in patients with rare diseases. The report also stimulates us to reassess the efficacy of biotin and thiamine in early infantile forms of BTBGD. Although the therapeutic benefit may seem doubtful in our case, the provision of closure and prognostication, along with implications of disease recurrence, were invaluable givings to the family.

Conflict of Interest
None declared.

Acknowledgment
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