



NEONATAL AND EARLY-INFANTILE BIOTIN-THIAMINE-RESPONSIVE BASAL GANGLIA DISEASE MIMICKING LEIGH SYNDROME: A CASE SERIES AND DIAGNOSTIC CLUES

Dr. Mundluru Yamini*, Dr. Dhurva Sandeep S.V^{2*}, Dr. Deepthi Shalma³

^{1,3}MD, Department of Paediatrics, PES Institute of Medical Sciences and Research (PESIMSR), Kuppam, Andhra Pradesh, India.

^{2*}MD, IAP PDF (Paediatric Neurology), Department of Paediatrics, PES Institute of Medical Sciences and Research (PESIMSR), Kuppam, Andhra Pradesh, India.

Email: ¹yamini.mundluru@gmail.com,

^{2*}dhurva.sandeep@gmail.com,

³Shalmadeepthi@gmail.com

Corresponding Author: Dr. Dhurva Sandeep S.V

MD, IAP PDF (Paediatric Neurology), Department of Paediatrics, PES Institute of Medical Sciences and Research (PESIMSR), Kuppam, Andhra Pradesh, India.

Email: dhurva.sandeep@gmail.com

ABSTRACT

Background: Biotin-thiamine-responsive basal ganglia disease (BTBGD), caused by biallelic pathogenic variants in SLC19A3, is a rare autosomal recessive neurometabolic disorder that is potentially reversible with early treatment. Neonatal and early-infantile forms may closely mimic Leigh syndrome, causing diagnostic delay.

Case presentation: We describe two children with early-onset BTBGD. Case 1 was a 23-day-old term female neonate from a third-degree consanguineous family with a previous unexplained infant death, who developed refractory seizures and central hypotonia. MRI showed extensive bilateral symmetrical lesions involving the basal ganglia, thalami, deep white matter and brainstem in a Leigh-like pattern. Whole-exome sequencing (WES) with copy-number analysis identified a homozygous contiguous SLC19A3 deletion. Case 2 was a 10-month-old male from a third-degree consanguineous family who had normal early development before developing excessive crying, dystonia, seizures and neuroregression. MRI demonstrated symmetrical basal ganglia and brainstem abnormalities with an elevated lactate peak on magnetic resonance spectroscopy (MRS). WES confirmed SLC19A3-related BTBGD.

Outcome: Both children received high-dose biotin and thiamine with supportive therapy and showed stabilization or improvement of acute neurological deterioration, although residual neurological deficits persisted.

Conclusion: Bilateral symmetrical basal ganglia and brainstem lesions in a neonate or infant with seizures, dystonia or neuroregression should prompt consideration of BTBGD, even when routine metabolic investigations are normal or only mildly abnormal. Empirical biotin and thiamine should be started promptly when the diagnosis is suspected rather than awaiting molecular confirmation.

Keywords: Biotin-Thiamine-Responsive Basal Ganglia Disease, SLC19A3, Leigh Syndrome, Neonatal Seizures, Neuroregression, Whole-Exome Sequencing.

INTRODUCTION

Biotin-thiamine-responsive basal ganglia disease (BTBGD), also termed thiamine metabolism dysfunction syndrome-2 (THMD2), is an autosomal recessive neurometabolic disorder caused by biallelic pathogenic variants in SLC19A3, which encodes human thiamine transporter-2 (hTHTR2) [1–5]. Impaired thiamine transport compromises cerebral energy metabolism and preferentially affects metabolically active structures including the basal ganglia, thalami and brainstem.

The disorder is potentially treatable, but neurological injury may become irreversible if treatment is delayed.

BTBGD has heterogeneous age-dependent phenotypes, including a neonatal Leigh-like presentation, a severe early-infantile form with seizures, dystonia and regression, the classical childhood encephalopathy phenotype, and a later Wernicke-like presentation [5–7]. Neonatal and early-infantile disease frequently overlaps clinically and radiologically with mitochondrial disorders, particularly Leigh syndrome. Routine biochemical investigations may be normal or show only mild abnormalities, whereas MRI typically demonstrates bilateral symmetrical basal ganglia involvement



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with variable thalamic, cortical, white-matter and brainstem lesions [6–10].

We report two early-life cases of genetically confirmed BTBGD presenting at different ages, highlighting the clinical spectrum, characteristic neuroimaging, diagnostic pitfalls and the importance of prompt disease-specific therapy.

MATERIALS AND METHODS

Study Design and Setting: This is a descriptive case series of two children with genetically confirmed SLC19A3-related BTBGD who were evaluated and managed in the Department of Paediatrics, PES Institute of Medical Sciences and Research (PESIMSR), Kuppam, Andhra Pradesh, India.

Clinical and Laboratory Evaluation: For each child, the family history (including consanguinity and sibling outcomes), perinatal history, developmental history, presenting features and neurological examination findings were recorded. Laboratory evaluation included blood lactate, plasma ammonia, venous blood gas analysis, blood and urine ketones, electrolytes and inflammatory markers, together with a sepsis screen and cerebrospinal fluid analysis and culture where clinically indicated. Electroencephalography (EEG) was performed where indicated.

Neuroimaging: Magnetic resonance imaging (MRI) of the brain was performed with T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) sequences, along with proton magnetic resonance spectroscopy (MRS).

Genetic testing: Whole-exome sequencing (WES) with copy-number variant analysis was performed in both children to establish the molecular diagnosis.

Treatment and follow-up: Both children received high-dose oral biotin (approximately 5 mg/kg/day) and thiamine (20–25 mg/kg/day) with supportive and symptomatic therapy. Clinical response, seizure control, movement disorder and neurodevelopmental status were assessed during hospital stay and at follow-up.

Ethical considerations: Institutional ethical approval was obtained according to institutional policy. Verbal informed consent for publication of clinical information and radiological images was obtained from the parents/legal guardians of both children.

RESULTS

Two children with genetically confirmed BTBGD were included: a neonate with a Leigh-like

phenotype (Case 1) and an infant with an early-infantile neuroregressive phenotype (Case 2). Their clinical, radiological, genetic and outcome features are described below and compared in Table 1.

Case 1: Neonatal Leigh-like phenotype

A 23-day-old term female neonate was admitted with recurrent abnormal movements consistent with seizures. She was the second child of a third-degree consanguineous couple. An elder female sibling had died at 10 months after recurrent seizures and progressive neurological deterioration and had been clinically suspected to have mitochondrial encephalopathy without molecular confirmation. The current pregnancy was evaluated antenatally; amniocentesis at 18 weeks showed normal FISH for chromosomes 13, 18, 21 and sex chromosomes, and no pathogenic variant was identified on the prenatal exome analysis available at that time.

She was delivered vaginally at 39 weeks + 4 days with a birth weight of 2.7 kg and Apgar scores of 7 and 9 at 1 and 5 minutes. The neonatal period was uncomplicated, with immediate crying, successful breastfeeding and discharge on day 4. At 23 days she developed recurrent four-limb abnormal movements without fever, gastrointestinal symptoms or other precipitating illness. Examination showed central hypotonia with preserved spontaneous activity and cry, brisk deep-tendon reflexes and no focal cranial nerve deficit.

Sepsis and metabolic evaluation did not identify an alternative cause. CSF was essentially non-inflammatory and cultures were sterile. Blood lactate was mildly elevated at 26 mg/dL, ammonia was 120 µmol/L and venous blood gas showed pH 7.33 with bicarbonate 15.3 mmol/L; electrolytes, ketones and inflammatory markers were otherwise not contributory. The principal differentials were Leigh syndrome, maple syrup urine disease, pyridoxine-dependent epilepsy, neonatal sepsis/meningitis and other inherited metabolic disorders.

Seizures persisted despite phenobarbitone and phenytoin, requiring intubation and mechanical ventilation. A therapeutic intravenous pyridoxine trial was given; overt seizures subsequently ceased. MRI showed extensive bilateral symmetrical diffusion restriction involving the thalami, lentiform nuclei, deep frontal white matter/centrum semiovale, corticospinal tracts, midbrain tegmentum, cerebral peduncles and pons (Figure 1). The lesions were T1 hypointense and T2/FLAIR and DWI hyperintense with corresponding ADC hypointensity, producing a Leigh-like metabolic pattern. MRS showed an inverted lactate peak (Figure 2).

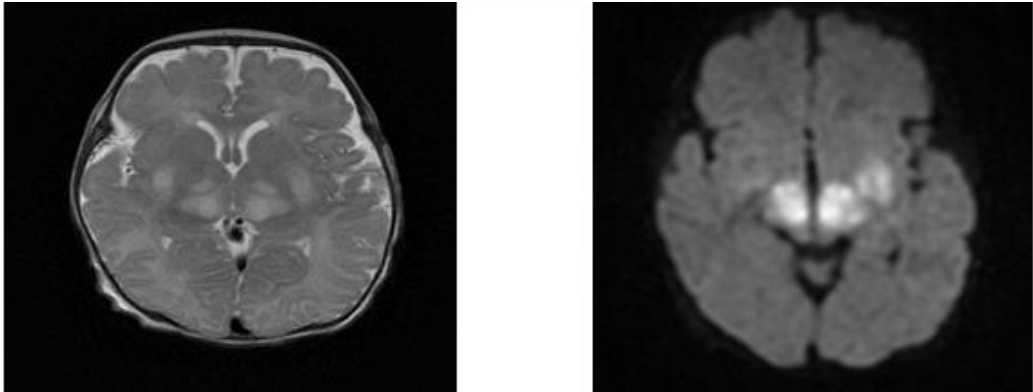


Figure 1. MRI Brain of Case 1 Showing Bilateral Symmetrical Diffusion Restriction Involving the Thalami, Lentiform Nuclei, Deep Frontal White Matter, Corticospinal Tracts, Cerebral Peduncles and Pontine/Midbrain Structures

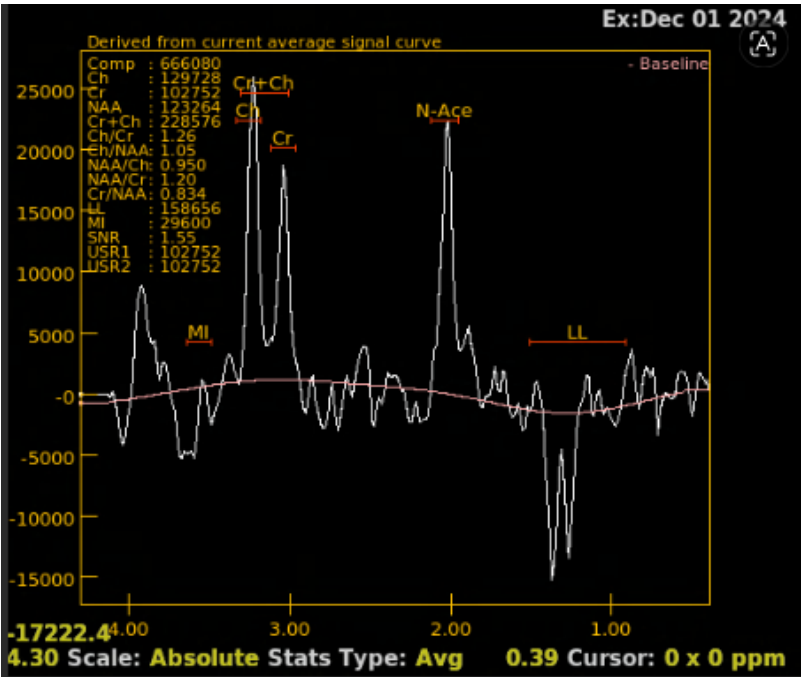


Figure 2. MR Spectroscopy of Case 1 Showing an Inverted Lactate Peak, Consistent With Impaired Cerebral Oxidative Metabolism.

Because of the characteristic imaging pattern and family history, WES with copy-number analysis was performed. It demonstrated a homozygous contiguous deletion of approximately 41.23 kb on

chromosome 2q36.3 encompassing SLC19A3, classified as likely pathogenic and diagnostic of THMD2/BTBGD (OMIM #607483) (Figure 3).

Variant	Zygosity	Size (KB)	Disease (OMIM)	Inheritance	Classification [§]
chr2:g.(?_227687397)_(227728625_?)del	Homozygous	41.23	-	-	Likely Pathogenic

Figure 3. Whole-Exome Sequencing/Copy-Number Analysis in Case 1 Demonstrating a Homozygous Contiguous Deletion Involving SLC19A3 on Chromosome 2q36.3.

Disease-specific therapy was initiated with oral biotin approximately 5 mg/kg/day and thiamine approximately 20 mg/kg/day, together with

levocarnitine, coenzyme Q10/B-complex supplementation, trihexyphenidyl and phenytoin. At follow-up, generalized seizures had not recurred and

feeding and weight gain were satisfactory; however, dystonic episodes, axial hypotonia, appendicular hypertonia, brisk reflexes, poor visual fixation and reduced spontaneous motor repertoire persisted. Multidisciplinary neurodevelopmental rehabilitation was continued.

Case 2: Early-Infantile Neuroregressive Phenotype

A 10-month-old male infant, the third child of a third-degree consanguineous couple, presented with excessive crying, abnormal involuntary movements and progressive neuroregression. There was no family history of similar illness. He had been born at term by vaginal delivery with a birth weight of 3.16 kg and had achieved age-appropriate developmental milestones during early infancy. Maternal hypothyroidism had been appropriately treated during pregnancy.

Approximately 20 days before admission, he developed persistent excessive crying and brief episodes of generalized tonic-clonic movements with upward eye deviation. Over subsequent days he became increasingly irritable, fed poorly, slept less and lost previously acquired developmental skills. The parents reported an apparent increase in the frequency and severity of abnormal movements after a recent DPT vaccination, although the neurological symptoms had started before

vaccination and a causal relationship could not be established.

On examination he was irritable but haemodynamically stable. Neurological examination showed developmental regression with loss of visual fixation/tracking and impaired recognition of his mother, mild generalized hypertonia, exaggerated reflexes, a positive striatal toe and intermittent dystonic posturing. Leigh syndrome, BTBGD, MELAS, other mitochondrial encephalopathies and selected inborn errors of metabolism were considered.

Routine investigations were largely non-specific. Blood lactate was 34 mg/dL; plasma ammonia was 92 μ mol/L, blood and urine ketones were not significantly abnormal, and venous blood gas showed pH 7.36 with bicarbonate 21.4 mmol/L. EEG showed an abnormal background with right centro-parietal epileptiform discharges.

MRI demonstrated bilateral symmetrical T2/FLAIR hyperintense and T1 hypointense abnormalities involving the basal ganglia and brainstem, with subtle diffusion restriction in the bilateral peri-occipital cortex, periaqueductal midbrain and dentate nuclei. MRS showed an elevated lactate peak (Figure 4). The imaging pattern initially suggested a Leigh-like mitochondrial encephalopathy.

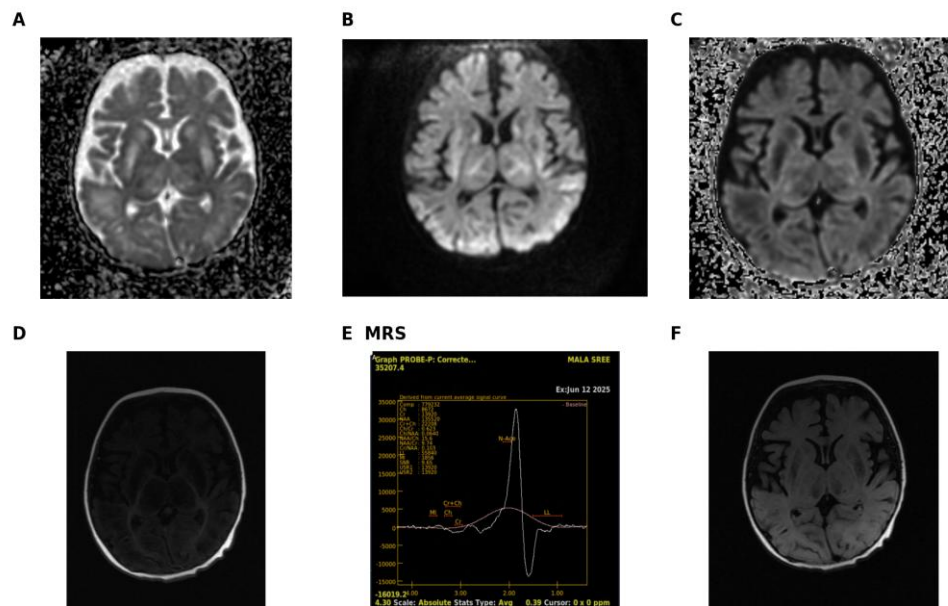


Figure 4. MRI/MRS of Case 2 Showing Bilateral Symmetrical Basal Ganglia and Brainstem Abnormalities With Additional Subtle Peri-Occipital, Periaqueductal and Dentate Involvement; MRS Demonstrates An Elevated/Inverted Lactate Peak.

Because BTBGD was considered on clinical and radiological grounds, high-dose biotin 5 mg/kg/day and thiamine 25 mg/kg/day were started empirically, together with levocarnitine, coenzyme Q10,

levetiracetam, clonazepam and trihexyphenidyl. WES subsequently demonstrated a homozygous contiguous deletion encompassing SLC19A3, confirming BTBGD (Figure 5

Gene* (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification ⁵
SLC19A3 (-) (ENST00000644224.2)	Exon 3	c.593T>C (p.Phe198Ser)	Homozygous	Thiamine metabolism dysfunction syndrome 2 (biotin/thiamine-responsive basal ganglia disease type) (OMIM#607483)	Autosomal recessive	Uncertain Significance (PM2,PP3)

Figure 5. Whole-Exome Sequencing/Copy-Number Analysis of Case 2 Demonstrating a Homozygous Contiguous Deletion Involving SLC19A3, Confirming THMD2/BTBGD.

Following treatment, sensorium and irritability improved and seizures and dystonic movements became less frequent. Visual fixation and tracking remained absent at discharge. At approximately 1 year 3 months, the child had developmental delay;

he could hold his neck and roll over and produced cooing sounds, while dystonic movements had decreased. Lifelong biotin and thiamine therapy, neurological follow-up and rehabilitation were planned.

Comparison of the two cases

Table 1. Comparison of Clinical, Metabolic, Radiological, Genetic and Outcome Features of the Two Cases

Feature	Case 1	Case 2
Age/sex	23 days; female	10 months; male
Phenotype	Neonatal Leigh-like; refractory seizures, hypotonia	Early-infantile; dystonia, seizures, neuroregression
Family context	Third-degree consanguinity; previous unexplained sibling death	Third-degree consanguinity; no similar family history
Metabolic profile	Mild lactate/ammonia elevation; transient acidosis	Largely non-specific; lactate elevated
MRI	Thalami, lentiform nuclei, deep frontal white matter, corticospinal tracts, midbrain and pons; diffusion restriction	Basal ganglia and brainstem with subtle peri-occipital, periaqueductal and dentate involvement
MRS	Inverted lactate peak	Elevated/inverted lactate peak
Genetics	Homozygous ~41.23-kb contiguous SLC19A3 deletion	Homozygous contiguous deletion encompassing SLC19A3
Treatment/outcome	Biotin + thiamine; seizures controlled; persistent motor/visual deficits	Biotin + thiamine; acute improvement; persistent visual/developmental deficits

DISCUSSION

This case series demonstrates two clinically distinct early-life presentations of SLC19A3-related BTBGD. The neonatal patient presented with refractory seizures and hypotonia within the first month of life, whereas the older infant had initially normal development followed by dystonia, seizures and rapid neuroregression. Despite the different presentations, both showed the characteristic bilateral symmetrical involvement of deep grey matter and brainstem structures on MRI, supporting the concept of a phenotypic spectrum rather than separate disorders.

The main diagnostic challenge is the close overlap with mitochondrial disease, particularly Leigh syndrome. Both patients had neurological manifestations and imaging findings compatible with Leigh syndrome, and both had lactate abnormalities. However, routine biochemical abnormalities were mild or non-specific. In

BTBGD, MRI may provide the earliest and most useful clue, especially when bilateral symmetrical basal ganglia lesions occur with variable thalamic, cortical, white-matter and brainstem involvement [6–10]. The neonatal case showed a more extensive pattern involving thalami, deep white matter, corticospinal tracts, midbrain and pons, whereas the infantile case had predominant basal ganglia/brainstem disease with additional subtle cortical, periaqueductal and dentate involvement. Family history and consanguinity were important clues. The first child had an elder sibling who died after a similar progressive neurological illness, while both families were consanguineous, consistent with autosomal recessive inheritance [4,11,12]. Molecular confirmation is therefore important not only for diagnosis but also for carrier testing, recurrence-risk assessment and prenatal counselling.

A particularly important practical point is that treatment should not be delayed while awaiting genetic results. Once BTBGD is suspected, high-dose biotin and thiamine can be started empirically because the disorder is potentially reversible and delayed treatment is associated with irreversible neurological injury [4,5,9]. In the present series, both children stabilized or improved after disease-specific therapy, but residual neurological deficits remained, suggesting that treatment was instituted after significant neuronal injury had already occurred.

The second child's deterioration was temporally associated with DPT vaccination according to parental observation, but symptoms had begun before vaccination and causality cannot be inferred. Physiological stressors such as fever, infection, fasting or other metabolic stress may precipitate decompensation in susceptible children; therefore, this observation should be interpreted cautiously. The main strength of this series is the direct comparison of neonatal and early-infantile phenotypes with detailed neuroimaging and molecular confirmation. Limitations include the very small sample size and relatively short follow-up, which preclude conclusions about genotype-phenotype correlations or long-term prognosis.

CONCLUSION

BTBGD should be considered in neonates and infants with refractory seizures, dystonia, encephalopathy or rapid neuroregression, particularly when there is consanguinity or an unexplained sibling death. Bilateral symmetrical basal ganglia and brainstem lesions on MRI, even with normal or mildly abnormal routine metabolic investigations, should prompt consideration of SLC19A3-related disease. Molecular testing with copy-number analysis is important for confirmation, but empirical high-dose biotin and thiamine should be initiated promptly when the clinical and radiological phenotype is suggestive. Early recognition offers an opportunity to prevent further irreversible neurological injury.

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Conflict of Interest Statement

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