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BEYOND PRRT2: DISCOVERY OF TREATABLE BIOTINIDASE DEFICIENCY IN AN INFANT WITH REFRACTORY FOCAL SEIZURES

Paediatrics

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ABSTRACT

Background: Biotinidase deficiency (BTD) is an autosomal-recessive neurometabolic disorder that manifests with multisystem neurological dysfunction when untreated. Early recognition enables complete reversibility with biotin supplementation. **Case Presentation:** We report a male infant with developmental delay, cortical visual impairment, progressive squint, and early-onset focal epilepsy. Serological evaluation showed reduced biotinidase activity (1.53; reference >5) despite normal serum biotin. Genetic testing revealed a homozygous pathogenic **BTD variant (c.641C>T; p.Thr214Ile)** and a heterozygous **PRRT2 pathogenic frameshift variant (c.649dup; p.Arg217ProfsTer8)**. EEG demonstrated frontally predominant generalized epileptiform discharges, with abnormal VEP responses. Neuroimaging was normal. **Management & Outcome:** High-dose biotin therapy was initiated with counselling for long-term supplementation and family screening. Early follow-up indicated reduction in seizure frequency and improved alertness. **Conclusion:** This case underscores the importance of considering biotinidase deficiency in infants with seizures and developmental delay despite normal MRI, and highlights the interpretive relevance of dual-gene findings.

KEYWORDS

Biotinidase deficiency, early-onset epilepsy, BTD gene, PRRT2, cortical visual impairment, developmental delay.

INTRODUCTION

Biotinidase deficiency (BTD) is an autosomal-recessive metabolic disorder resulting from impaired recycling of the essential cofactor biotin.^1^ The disorder manifests with seizures, hypotonia, developmental delay, visual impairment, alopecia, and sensorineural hearing loss when untreated.^2^ Early diagnosis is crucial because oral biotin supplementation fully prevents neurological sequelae.^3^ While newborn screening programmes detect most affected infants, partial or late-onset presentations may remain unrecognized.^4^ Genetic heterogeneity and varying biochemical profiles add further diagnostic complexity.

The coexistence of pathogenic variants in seizure-associated genes, such as **PRRT2**, may modify or complicate the phenotype.^5^ PRRT2-related disorders typically include benign familial infantile seizures and paroxysmal kinesigenic dyskinesia.^6^ We present an infant with combined BTD and PRRT2 variants presenting with early-onset epilepsy, developmental delay, and cortical visual impairment, highlighting diagnostic challenges and management considerations.

Case Report

A male infant, presented with concerns of global developmental delay-particularly impaired motor and language milestones-and visual inattentiveness since early infancy. Parents also noted progressive squint and recurrent focal seizures beginning in the first months of life. Seizures were brief focal events with clusters of multifocal semiology, occurring several times per week. A positive family history of seizures was present in the maternal grandfather.

Neurological examination revealed poor visual fixation, intermittent esotropia, mild axial hypotonia, and delayed social-communication milestones. There were no dysmorphic features or cutaneous stigmata. Systemic examination was unremarkable.

Video-EEG showed **frontally predominant generalized epileptiform abnormalities**. Visual evoked potentials demonstrated **poorly formed waveforms**, consistent with cortical visual impairment. MRI brain was normal.

Given the multisystem neurological presentation, metabolic evaluation was pursued. Serum **biotin level was normal (0.52 ng/mL; reference 0.1–2.46)**. However, **biotinidase enzyme level was significantly reduced (1.53; reference >5)**, raising suspicion for biotinidase deficiency despite normal biotin levels.

Comprehensive genomic analysis identified a **homozygous pathogenic variant in the BTD gene: c.641C>T (p.Thr214Ile)**, reported at extremely low allele frequency in population datasets (gnomAD v2.1: 0.003%; v3.1: 0.001%) and previously associated with BTD deficiency.^7^ Functional prediction tools (SIFT, LRT, PolyPhen) indicated a damaging effect. The variant is listed in ClinVar (ID 156003) as **likely pathogenic**.

Additionally, a **heterozygous PRRT2 frameshift variant c.649dup (p.Arg217ProfsTer8)** was detected, classified as **pathogenic** due to loss-of-function (PVS1) and strong case-series evidence (PS4).^6^ This variant is associated with **benign familial infantile seizures-2** and **infantile convulsions with paroxysmal choreoathetosis**. The family history of seizures further supported segregational relevance.

A diagnosis of **biotinidase deficiency with coexisting PRRT2-related epilepsy** was established.

The infant was commenced on **biotin therapy at 10 mg/day**, with plans for dose escalation per clinical response. Antiseizure medications were optimized for focal epilepsy. Parents were counselled regarding lifelong biotin supplementation, the excellent prognosis with early treatment, and the autosomal-recessive inheritance pattern. Cascade testing for family members was recommended.

Early follow-up noted improved alertness and reduced seizure clustering. Long-term outcomes are being monitored.

DISCUSSION

BTD deficiency is easily treatable yet underdiagnosed when symptoms begin later or when biotin levels appear normal.^1,3^ This infant's presentation-developmental delay, cortical visual impairment, squint, and early-onset seizures-is consistent with profound BTD deficiency.^2^ The low biotinidase enzyme activity confirmed functional impairment even in the presence of normal serum biotin, as enzyme deficiency rather than biotin level predicts clinical severity.^8^

The identified **p.Thr214Ile BTD variant** has been previously documented in patients with symptomatic enzyme deficiency.^7^ Early supplementation prevents irreversible neurological damage, highlighting the importance of timely recognition.^3,4^

The coexistence of a pathogenic **PRRT2** variant adds diagnostic specificity regarding seizure predisposition. PRRT2 mutations typically cause benign familial infantile epilepsy but can coexist with other neurogenetic disorders, influencing seizure phenotype.^5,6^ In this case, more severe seizure burden may partially relate to the uncorrected metabolic dysfunction.

This case illustrates the synergistic value of enzyme assays and genomic testing in infants with unexplained epilepsy and developmental delay, even with normal neuroimaging.

CONCLUSION

This report emphasizes that **biotinidase deficiency should be considered in any infant with early-onset seizures, developmental delay, and unexplained visual impairment**, even when MRI is normal. Early biotin supplementation results in substantial clinical

improvement. The coexistence of PRRT2-related epilepsy underscores the importance of comprehensive genetic testing. Early recognition and treatment can significantly alter developmental trajectories.

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