


Biotinidase Deficiency in Children: Clinical Outcomes and Neuroimaging Correlations

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ABSTRACT

Objectives: Biotinidase Deficiency (BTD) is an autosomal recessive metabolic disorder caused by mutations in the BTD gene, leading to impaired Biotin metabolism and resulting in severe neurological impairments, including seizures and developmental delays. Early diagnosis and treatment are crucial for improving patient outcomes.

This study aims to investigate the clinical outcomes and neuroimaging findings in pediatric patients diagnosed with BTD, emphasizing the importance of early detection and multidisciplinary management.

Materials & Methods: This retrospective review was conducted over seven years, analyzing medical records of five patients diagnosed with BTD based on clinical, radiological, and genetic criteria. Brain MRIs were performed, and genetic analyses confirmed the presence of pathogenic mutations in the BTD gene.

Results: All patients exhibited characteristic clinical symptoms of BTD, including seizures and developmental delays. MRI findings revealed bilateral symmetrical increased signal intensity on T2-weighted images and low signal intensity on T1-weighted images in subcortical white matter. Treatment with Biotin resolved seizures in all cases; however, irreversible complications such as sensorineural hearing loss were noted in three patients. Early initiation of Biotin therapy correlated with better clinical outcomes.

Conclusion: This study highlights the necessity of a multidisciplinary approach to managing BTD, integrating genetic testing, clinical assessments, and neuroimaging. Early diagnosis through newborn screening is vital for improving long-term outcomes in affected children. Future studies should focus on expanding screening initiatives and investigating long-term treatment effects.

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Introduction

Biotinidase Deficiency (BTD) is an inborn error of metabolism with autosomal recessive inheritance. BTD gene mutations result in reduced or absent Biotinidase activity. BTD has an incidence of 1:40,000 to 1:60,000 births in the world (1). The clinical features of

untreated severe BTD may include developmental delays, seizures, hypotonia, ataxia, skin rashes, and hearing impairment. Approximately 75% of untreated, symptomatic children with profound BTD have permanent sensorineural hearing loss that does not improve with biotin treatment, which may eventually require cochlear implants (2, 3). Early diagnosis plays

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a critical role in the management of BTB, as it has previously been observed that patients who receive treatment before symptoms developed, have normal development (4-6). The BTB gene, located on chromosome 3q25, has been the subject of extensive research, identifying more than 150 mutations linked to BTB (7). The most prevalent mutations are c.1330G>C (p.D444H), c.755A>G (p.D252G), and c.[1330G>C;511G>A] (p. [D444H; A171T]) (8). Profound BTB is characterized by less than 10% of normal Biotinidase activity, typically resulting from severe mutations in homozygous or compound heterozygous forms. In contrast, partial BTB is defined by 10%-30% of normal activity, often arising from compound heterozygosity, including one severe mutation and one less severe variant. The BTB genotype and clinical course do not always demonstrate consistency (9). Although Newborn Screening (NBS) is implemented in several countries worldwide, it is not widely used in the South-East Asian and Eastern Mediterranean regions (2). Thus, diagnosis of BTB in many countries is suspected after clinical symptoms have been developed. Besides, brain imaging plays a crucial role in early diagnosis. Diagnosis can be confirmed by measuring serum Biotinidase activity levels or genetic studies (2, 6). The most common findings in brain MRIs of the affected individuals include leukoencephalopathy, ventriculomegaly, and brain atrophy. However, approximately 21% of patients have normal brain imaging. Therefore, a normal brain MRI cannot exclude BTB (2). Accordingly, this study aimed to investigate probable unusual findings among affected patients with BTB according to the MRI followed by genetic testing.

Materials & Methods

This retrospective study conducted over seven years, reviewed the medical records of patients who displayed clinical, radiological, and genetic indicators consistent with BTB. Five patients with confirmed BTB diagnosis and accessible brain MRI were selected for this study. All patients presented with BTB symptoms between 2016 to 2023. Diagnosis is confirmed by comprehensive clinical assessment followed by genetic analysis. MR images were acquired on a 1.5 Tesla scanner. The local ethics committee approved the study, including the use of the data for future research. Additionally, informed consent was obtained from the patients' parents. The diagnosis of BTB was confirmed by the presence of the responsible gene mutation through whole exome sequencing followed by bioinformatics analysis.

Results

The study's objectives were to document the initial clinical of the patients (see Table 1), their imaging findings (Figure 1), and their subsequent outcomes. Case #1 was a 2-month-old male presented with clonic seizures from one month old, hair loss, and hypotonia. He was the third child (3 of 3) of parents with consanguineous marriage. His gross motor development milestones were slightly delayed; however, other aspects of his development were otherwise normal. Brain MRI performed at two months of age demonstrates bilateral and symmetrical pathologic increased signal intensity on T2 images and low signal intensity on T1 images in anterior and posterior fossa in subcortical, deep white matter and periventricular areas. FLAIR images revealed signal suppression in the same geographical areas. No area of restriction was noted on DWI images. Based on clinical and MRI findings, he was treated with 5 mg of Biotin daily and the seizures vanished. Further genetic analysis revealed pathogenic homozygote BTB. A follow-up brain MRI conducted one year after the initiation of treatment; it revealed no pathological signal intensity in the brain parenchyma.

Case #2 was a 1-year-old male child, the first baby of a consanguineous marriage presented with clonic seizures starting from two months old, hearing abnormality, alopecia, and a history of skin rashes. His neurodevelopmental milestones, specifically social skills were delayed. His hearing loss was of sensorineural type, and he later became a candidate for cochlear transplantation. The MR images performed over one year of age, showed bilateral and symmetrical pathologic increased signal intensity on T2 images and low attenuation on T1 images in anterior and posterior fossa in subcortical, deep white matter, and periventricular areas. Signal suppression was observed on FLAIR images in the same geographical area. Bilateral and symmetrical restriction in the posterior limb of the internal capsule was noted in DWI images with hypo intensity on ADC map at the same geographical areas. Likewise, as an incidental finding, IPH in the right occipital and right frontal was noted. Moreover, SDH was observed in the right hemisphere. MRI images demonstrate some extent of parenchymal volume loss. Tandem mass spectroscopy (MS/MS) was compatible with holocarboxylase deficiency.

Case #3 was a 1-year-old female child from a nonconsanguineous marriage presented with myoclonic seizures from two months old, hypotonia, head lag, and attention deficit. Her neurodevelopment was delayed. Her optic disc was pale on ophthalmoscopy indicating mild optic nerve atrophy. Brain MRI performed at two months of age showed bilateral and symmetrical pathologic increased signal

intensity in T2 images and low attenuation on T1 images in anterior and posterior fossa in subcortical, deep white matter, and periventricular areas. FLAIR images revealed signal suppression at the same geographical areas. No area of restriction was noted on DWI images. Seizure frequency was reduced after initiation of treatment with 5 mg Biotin twice daily. On serial follow-up, she developed microcephaly and hearing abnormality. The auditory brainstem reflex (ABR) exam was abnormal.

Case #4, a 2-year-old male, child of parents with consanguineous marriage, presented with aphonic cries from the first day of birth, as well as clonic seizures and alopecia from two months old. His neurodevelopmental milestones were also delayed. His problems with hearing started at five months old and

he started using hearing-aid devices at three years old. His treatment with 5 mg Biotin daily started at two months old and seizures vanished at 4-month-old. Brain MRI performed at three months of age shows bilateral and symmetrical pathologic increased signal intensity on T2 images and low attenuation on T1 images in anterior and posterior fossa in subcortical, deep white matter, and periventricular areas. No signal suppression was observed on FLAIR images. Bilateral and symmetrical restriction in internal capsules was noted in DWI images with hypo intensity on ADC map at the same geographical areas. As an incidental finding axial images demonstrate the prominence of the anterior subarachnoid space suggestive of benign subarachnoid space enlargement.

Table 1. Summary of clinical, imaging, and genetic findings in patients with BTD

Case #	Age	Gender	Clinical Presentation	MRI Findings	Medication(s)	Treatment Response
1	2 months	Male	Clonic seizures (from 1 month old), hair loss, hypotonia.	Bilateral symmetrical increased signal intensity on T2; low signal intensity on T1 in subcortical and deep white matter. signal suppression on FLAIR. No restriction on DWI.	5 mg Biotin daily	Seizures vanished.
2	1 year	Male	Clonic seizures (from 2 months old), hearing abnormalities, alopecia, skin rashes.	Bilateral symmetrical increased signal intensity on T2; low attenuation on T1; restriction in the posterior limb of the internal capsules on DWI; parenchymal volume loss	Biotin (dosage not specified)	Reduced seizure frequency Became a candidate for cochlear transplantation.
3	1 year	Female	Myoclonic seizures (from 2 months old), hypotonia, head lag, attention deficit.	Bilateral symmetrical increased signal intensity on T2; low attenuation on T1; signal suppression on FLAIR; no restriction on DWI.	Biotin (dosage not specified)	Reduced seizure frequency Developed microcephaly and hearing abnormality.
4	2 years	Male	Aphonic cries from birth, clonic seizures (from 2 months old), alopecia.	Bilateral symmetrical increased signal intensity on T2; low attenuation on T1; restriction in internal capsules on DWI; prominence of anterior subarachnoid space noted.	5 mg Biotin daily	Seizures vanished after treatment initiated at 2 months old.
5	2 days	Male	Clonic seizures, macrocephaly.	No signal intensity changes in white matter; mild brain atrophy (Evans index > 0.3).	5 mg Biotin daily from day 3	No seizure episodes ever since.

Case #5 was a 2-day-old male, a child of a consanguineous marriage, presented with clonic seizures and macrocephaly. Due to clinical suspicion, he received treatment with 5 mg daily Biotin from three days old, and he has had no episode of seizure ever since. Brain MRI performed at seven years of age demonstrated no signal intensity changes in white

matter. Mild parenchymal volume loss (Evans index greater than 0.3) was noted. No additional remarkable MRI finding was observed. His neurodevelopmental milestones were delayed in gross motor aspect as he started walking at two years old. Molecular genetic findings are summarized as Table 2.

Table 2. Molecular genetic findings in study cases

Patient ID	Gene	Accession number	Nucleotide/AA change	Zygoty	Pathogenicity
C1	BTD	NM_001370658.1	c.41_44del (p.Gly14Valfs*35)	Mutated Homozygous	Pathogenic
C2	BTD	NM_001370658.1	c.101_102del (p.Glu34Glyfs*2)	Mutated Homozygous	Likely
C3	BTD	NM_001370658.1	c.528_542del (p.Asn177_Ser181del)	Mutated Homozygous	Likely
C5	BTD	NM_001370658.1	c.40_41del (p.Gly14Leufs*17)	Mutated Homozygous	Pathogenic

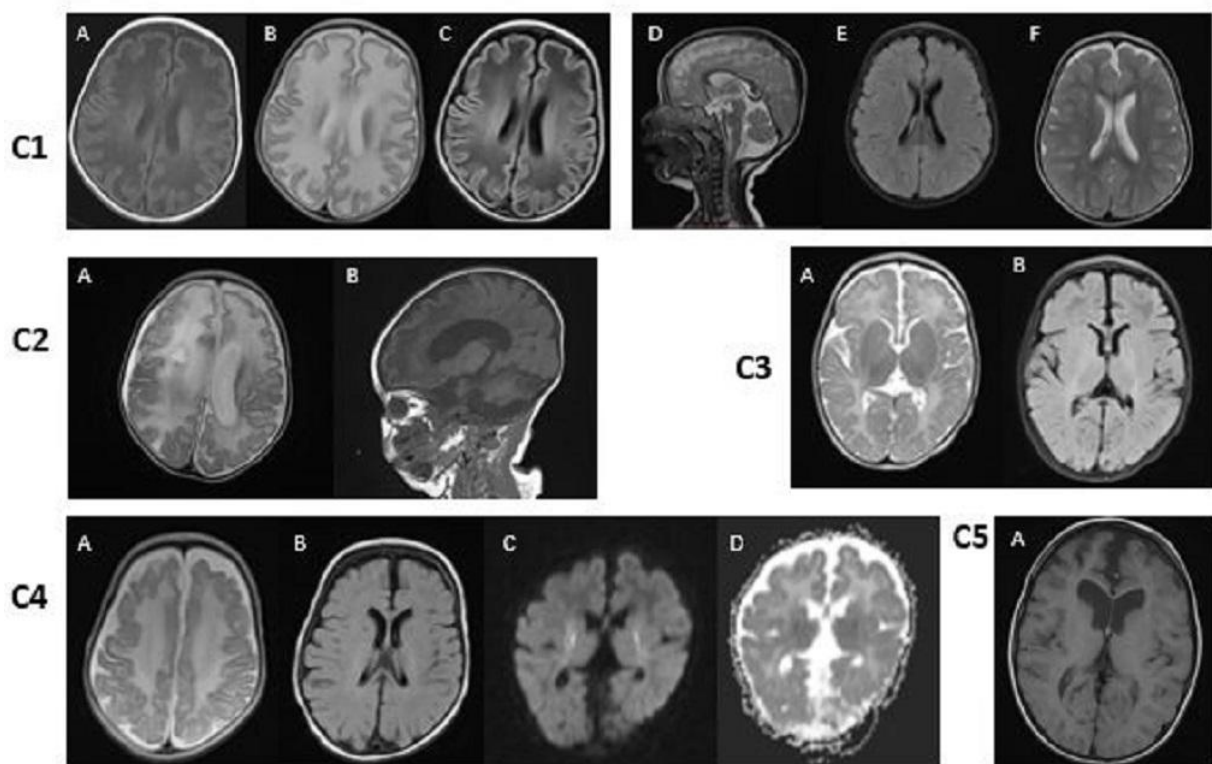


Figure 1. Imaging patterns in the studied BTM patients. Case 1: Axial T1 weighted (A), T2 weighted (B), and FLAIR (C) images show bilateral and symmetrical pathologic increased signal intensity on T2 image and low attenuation on T1 image in subcortical, deep white matter and periventricular areas with signal suppression on FLAIR image on the same geographical area. Sagittal T1 weighted (D), axial T2 weighted (E), and FLAIR (F) images show no remarkable finding indicating a normal study. Case 2: Axial T2 weighted (A) and coronal T1 weighted images show bilateral and symmetrical pathologic increased signal intensity on T2 image and low attenuation on T1 image in subcortical, deep white matter and periventricular areas. Case 3: Axial T2 weighted (A) and FLAIR (B) images show bilateral and symmetrical pathologic increased signal intensity on T2 image in subcortical, deep white matter and periventricular areas with signal suppression on FLAIR image in frontal white matter. Case 4: Axial T2 weighted (A) and FLAIR (B) images show bilateral and symmetrical pathologic increased signal intensity on T2 image in subcortical and deep white matter without signal suppression on the FLAIR image. DWI (C) and ADC map (D) images show bilateral and symmetrical restriction in internal capsules on DW image with hypo intensity on the ADC map at the same geographical areas. Case 5: Axial T1 weighted image shows mild parenchymal volume loss (Evans index greater than 0.3).

Discussion

BTM is an autosomal recessive disorder caused by mutations in the BTM gene, leading to impaired biotin metabolism. This deficiency can result in severe

neurological outcomes, including seizures, hypotonia, and developmental delays. MRI findings often reveal significant central nervous system abnormalities, such as demyelination and atrophy, correlating with clinical severity. Genetic analysis has identified various

pathogenic mutations within the BTD gene, with profound deficiencies, typically linked to more severe phenotypes. Early diagnosis and treatment with Biotin supplementation are crucial for improving clinical outcomes and mitigating long-term neurological damage in affected pediatric patients (10-12).

Previous studies have emphasized the importance of MRI findings in the diagnosis of BTD. This study set out with the aim of assessing the importance of MRI findings in the diagnosis of BTD in a series of five patients. The results of this study show that bilateral and symmetrical pathologic increased signal intensity on T2 images and low signal intensity on T1 images in subcortical, deep white matter and periventricular areas were noted in 4 of 5 cases representing cerebral edema. Imaging of These four patients was conducted at two months old or later. No signal abnormality was reported in Case 5, where Biotin treatment started in the early neonatal period. The reversibility of pathological signal intensities is demonstrated in Case 2, where the MRI results returned to normal one year following treatment. FLAIR images revealed decreased signal intensity in subcortical, deep white matter and periventricular areas (Signal suppression) in one case (Case 3). Areas of restricted diffusion with ADC correlation were noted in two cases in the basal ganglia and posterior limb of the internal capsule.

Ranjan et al. (2019) and Desai et al. (2008) who also found reduced diffusion in the brain stem, middle cerebellar peduncles, splenium of the corpus callosum, posterior limbs of the internal capsules, corona radiata, and parieto-occipital white matter (3, 13, 14). These results are consistent with other research, which found diffuse white matter edema as a common imaging finding in young infants with BTD (15, 16). Although clinical usage has not been methodologically validated, occasional flair suppression can also be observed in tumefactive multiple sclerosis as a combined effect of severe myelin loss, necrosis, and reactive gliosis (17).

After initiating Biotin replacement, seizures have been controlled in all cases. However, improvement in other symptoms, specifically neurodevelopmental abnormalities depend on the time of treatment initiation. Perhaps the most interesting result was near normal MR imaging of Case 5 in which treatment had been started empirically three days after birth based on clinical suspicion. This finding is consistent with that of Desai (2008) who reported near complete resolution of signal abnormalities in two patients with BTD after

treatment (13). Hearing abnormalities were observed in three patients. Sensorineural hearing loss was irreversible and has not improved after treatment with Biotin. These results are in line with those of previous studies (13, 18).

BTD should be considered in infants presenting with seizures and developmental delay, as early Biotin therapy can prevent irreversible complications. Retrospective screening and genetic analysis confirmed the diagnosis in two cases, with marked clinical improvement post-treatment. These findings support revisiting newborn screening policies, particularly in diverse populations (19).

In Conclusion

Early diagnosis and treatment of BTD are crucial to prevent irreversible complications such as hearing loss. This study highlights the value of integrating clinical evaluation, neuroimaging, and genetic assessment mainly in regions with no access to routine newborn screening. Interpreting MRI findings along with neurological symptoms, supporting the role of imaging in diagnosis. Expanding screening and monitoring can significantly improve personalized care and long-term outcomes.

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Authors' Contributions

Farrokh Seilanian Toosi and Mohsen Saberifar contributed to the acquisition, analysis, and interpretation of neuroimaging data, including MRI evaluations and correlation with clinical outcomes. NA performed and validated genetic analyses to confirm BTD diagnoses. Narges Hashemi conducted clinical assessments, collected patient data, and evaluated treatment responses. Mehran Beiraghi Toosi conceptualized and designed the study, supervised the research process, integrated multidisciplinary findings, and drafted the manuscript. All authors critically reviewed, revised, and approved the final manuscript for submission.

Conflict of Interest

The authors declared no conflict of interest.

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