DOI: 10.7860/JCDR/2025/77288.21926

Case Report

Paediatrics Section

Severe Biotinidase Deficiency in a Newborn Due to a Novel Mutation: A Case Report

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ABSTRACT

Hyperammonaemia is one of the common causes of early neonatal deterioration. Inborn errors of metabolism are frequent contributors to hyperammonaemia in newborns. Profound biotinidase deficiency is a rare cause that closely mimics inborn errors of metabolism. This report describes a rare case of profound biotinidase deficiency presenting as deterioration in the early neonatal period, characterised by hyperammonaemia, acidosis, hypoglycaemia, and ketosis. A three-day-old male patient presented with poor feeding and vomiting for six hours, along with respiratory difficulty for the same duration. The baby was hypotonic, exhibiting weak plantar and palmar grasp reflexes, poor sucking reflex, and reduced Moro reflex. The differential diagnoses considered included early onset sepsis and inborn errors of metabolism; however, the sepsis screen was negative. Blood investigations revealed severe metabolic acidosis, hyperammonaemia, hypoglycaemia, and ketonuria. Acyl carnitine levels (C5-OH) were above normal, and serum biotinidase levels were very low. This patient was diagnosed with severe biotinidase deficiency, and genetic analysis revealed a rare homozygous nonsense mutation in the Biotinidase (BTD) gene. This mutation led to a profound deficiency of the biotinidase enzyme, resulting in early neurological complaints. After the initial stabilisation of the baby, he was started on biotin supplementation and was placed under regular follow-up. Profound biotinidase deficiency should be considered as one of the causes of early neonatal deterioration. The management of profound deficiencies involves treating the acute presentation while correcting acid-base imbalances, hypoglycaemia, and related issues. The mainstay of long-term treatment is lifelong biotin supplementation.

Keywords: Biotin supplementation, Biotinidase *(BTD)* gene, Hyperammonaemia, Organic acidaemia

CASE REPORT

A three-day-old male neonate, born to parents in a third-degree consanguineous marriage, was brought to the department of Paediatrics at the hospital with chief complaints of poor feeding and vomiting for six hours, along with breathing difficulty for two hours. The baby had been otherwise healthy until six hours prior. He had taken breast milk normally until day two of life but became lethargic and unable to suck adequately by day three. Before presenting to the hospital, the baby experienced four episodes of vomiting, which contained only milk particles. The infant was born via Lower Segment Caesarean Section (LSCS) at 38 weeks of gestational age, weighing 3 kg. The mother did not have any comorbidities and had no significant infections or substance abuse during the antenatal period.

On examination, the baby appeared dull with poor activity and a poor sucking reflex. He exhibited tachycardia (178 beats/min), tachypnoea (74/min), and hypotension (mean arterial pressure of 32 mm Hg). The baby was hypotonic with weak plantar grasp, palmar grasp, and reduced Moro reflex. Abdominal examination did not reveal any organomegaly. Cardiovascular examination did not indicate any murmurs or added sounds, and respiratory system examination was normal, aside from the increased respiratory rate and work of breathing.

Arterial blood gas analysis revealed severe metabolic acidosis, hypoglycaemia (38 mg/dL), and elevated ammonia levels (240 µmol/L). Ketonuria was present, with a pH of 7.12 and low bicarbonate levels (11 mmol/L) [Table/Fig-1].

Blood parameters	Results	Normal range
Haemoglobin	17.2 g/dL	14-22 g/dL
Total leucocyte count	12330 cells/ cubic mm	9000-30000 cells/cubic mm
Platelet counts	2,63,000 cells/ cubic mm	1,50,000-4,50,000 cells/cubic mm
C-Reactive protein	1.5 mg/L	<6 mg/L
Serum blood glucose	38 mg/dL	70-100 mg/dL
Serum ammonia	240 µmol/L	21-95 µmol/L
Urine ketones	Positive	Negative
pH in Arterial Blood Gas analysis (ABG)	7.12	7.35-7.45
$paCO_2$ in ABG	30 mmHg	35-45 mmHg
paO_2 in ABG	87 mmHg	60-110 mmHg
Bicarbonate in ABG	11 mmol/L	22-26 mmol/L
Acylcarnitine profile	1.08 µM	0.05-1.0 µM
Serum biotinidase	0.83 nmol/mL/ min	5.5-17.10 nmol/mL/min Partial deficiency: 1.10-3.30 nmol/mL/min Profound deficiency: <1.10 nmol/mL/min Carriers: 2.70-8 nmol/mL/min

[Table/Fig-1]: Laboratory investigations.

The common differential diagnoses for hyperammonaemia in newborns include urea cycle defects, organic acidaemias, fatty acid oxidation defects, congenital lactic acidosis, and transient hyperammonaemia of newborns. Since the baby presented with symptoms after 24 hours, the transient cause was ruled out. The presence of metabolic acidosis and ketosis, along with hyperammonaemia, indicated that organic acidaemias or fatty acid oxidation defects could be the possible causes. Consequently, an acylcarnitine profile was sent, which revealed an elevated level (1.08 µM) of 3-hydroxy isovaleryl carnitine (C5OH). A urine analysis for organic acids and serum biotinidase levels was also performed to investigate potential biotin deficiency. The serum biotinidase levels were found to be low (0.83 nmol/mL/min). Subsequently, genetic testing for mutations in the Biotinidase (BTD) gene was conducted. The results showed a homozygous nonsense mutation, c.1461G>A,

in exon 4 (Ref: NM_000060.3 and NP_000051.1), signifying a mutation in the BTD gene (p.W487X).

The baby was initially managed with ventilatory support, intravenous glucose (10% dextrose at 5 mL/kg to 15 mL as a stat dose, followed by maintenance intravenous dextrose), bicarbonate therapy (3 mmol slow intravenous bolus at a dose of 1 mmol per kg as a stat dose, with further corrections guided by blood gas analysis), and biotin (5 mg per day). The baby recovered from the acute illness and was discharged after 12 days of hospitalisation. Upon follow-up at six months of age, the baby displayed normal development. The baby was advised to continue biotin supplementation (5 mg per day) for life and to attend regular follow-ups to monitor for skin manifestations, neurological issues, growth, and development. The scanned copy of the genetic report has been mentioned at the end.

DISCUSSION

Sudden deterioration in the immediate neonatal period is multifactorial, with sepsis being the most common cause. Once sepsis is ruled out, other potential causes include inborn errors of metabolism, duct-dependent lesions, and congenital adrenal hyperplasia. The initial screening investigations recommended are arterial blood gas analysis, serum ammonia levels, serum lactate levels, blood sugar levels, urine ketones, and reducing substances [1].

Hyperammonaemia is one of the most common indicators of inborn errors in metabolism. Common causes of hyperammonaemia include transient hyperammonaemia of the newborn, defects in the urea cycle, organic academia, fatty acid oxidation defects, congenital lactic acidosis, and defects in pyruvate metabolism, among others [1]. The patient's further workup is guided by various parameters, including the presence or absence of acidosis and ketosis, and is based on the anion gap.

Severe biotinidase deficiency is a rare cause of hyperammonaemia presenting in the early neonatal period. Biotinidase is an enzyme that cleaves biotin from dietary protein sources and recycles it to deliver its metabolic functions. Biotin acts as a co-factor for various carboxylase enzymes involved in gluconeogenesis, fatty acid metabolism, and amino acid metabolism [2].

Biotinidase deficiency can be classified as either partial or profound. A partial deficiency is defined as 10-30% of the normal serum activity of biotinidase, while a profound deficiency is defined as less than 10% of the normal serum activity [3]. The incidence of partial deficiency is approximately one in 110,000, whereas the incidence of profound deficiency is about one in 137,000 [4]. Partial deficiency typically presents in infancy or early childhood with various skin manifestations, including dermatitis, alopecia, and eczema, along with neurological symptoms such as lethargy, hypotonia, and poor developmental milestones. In contrast, profound deficiency presents in the early neonatal period as sudden deterioration with hyperammonaemia, hypoglycaemia, metabolic acidosis, ketosis, neonatal seizures, and apnea [5].

A study from North India (n=10) showed a male preponderance (80%). The median age at presentation in that cohort was six months (ranging from 1 month to 84 months). Seizures were observed in 90% of patients; however, seizures were not present in this case. Hypotonia was noted in 70% of patients, whereas alopecia was seen in 90% of them. Lactate levels were increased in 40% of patients, and ammonia levels were elevated in 30% [6]. A case report described a three-day-old neonate who presented with breathlessness and had increased lactate and ammonia levels and was subsequently diagnosed with biotinidase deficiency [7]. Another case report detailed a four-month-old infant who presented with seizures, vomiting, alopecia, and poor weight gain [8]. A further case report involved a three-year-old girl who exhibited symptoms of recurrent respiratory tract infections and oral candidiasis, along with sensory neural hearing loss [9]. All of the aforementioned literature illustrates that the age of presentation is highly variable, ranging from the neonatal age group to young childhood. Presenting complaints in neonates and infants are most commonly neurological, while the presenting complaints in young children are predominantly non-neurological, such as recurrent infections and skin changes.

Biotinidase deficiency can be categorised as partial or profound due to various mutations in the BTD gene, which is located on chromosome 3p25. These mutations typically follow an autosomal recessive pattern of inheritance [10]. The serum biotinidase levels in this patient were very low (0.83 nmol/mL/min). Such low levels are usually associated with homozygous frameshift or nonsense mutations that lead to the complete truncation of the protein, resulting in very low activity of the biotinidase enzyme. More than 165 different mutations in the BTD gene have been documented, linked to both partial and profound deficiencies [5]. The most common mutation reported is in exon 4 of the BTD gene, which is c.1330G>C (p.D444H) [11-13]. This is a missense point mutation where guanine is replaced by cytosine at codon 1330, leading to an amino acid change from aspartate to histidine at position 444. This mutation typically causes only a partial deficiency. In the patient discussed, the mutation identified is homozygous at c.1461G>A (p.W487X) in exon 4. This is a nonsense point mutation where guanine is replaced with adenosine at codon 1461, leading to an unknown amino acid structure at position 487. This particular mutation has not been described in previously published literature. The unknown amino acid that has been inserted at position 487 could potentially cause complete truncation of the protein, resulting in very low activity of biotinidase and thereby leading to profound deficiency.

A study involving 10 patients with biotinidase deficiency reported a median level of 0.3 nmol/mL/min (range: 0 nmol/mL/min to 1.67 nmol/mL/min). None of the patients in that study underwent genetic testing [6]. In another case report involving a three-year-old girl, the biotinidase levels were found to be 1.6 nmol/mL/min. This patient underwent genetic testing, which identified a heterozygous mutation (R157H) in the biotinidase gene [9]. Patients with a heterozygous mutation typically present with non-neurological symptoms at an older age, as they only exhibit a partial deficiency. In contrast, patients with a homozygous mutation, like our patient, tend to manifest neurological symptoms in the neonatal or infantile period, exhibiting profound deficiency of the enzyme due to the homozygous mutation.

Management of profound deficiency involves treating the acute presentation while addressing acid-base imbalances, hypoglycaemia, and other relevant issues. The mainstay of long-term treatment is lifelong biotin supplementation. Patients must be regularly followed up to monitor for signs of deficiency, including skin manifestations (e.g., eczematous skin rash, alopecia, candidiasis), neurological manifestations (e.g., hypotonia, ataxia, seizures), ophthalmic manifestations (e.g., optic atrophy, scotomas), hearing loss, poor growth, and recurrent infections. Parents should be advised to avoid raw eggs in the diet, as raw eggs bind to biotin and reduce its bioavailability. Genetic counseling should also be discussed. Most importantly, ensuring adherence to biotin therapy at each follow-up visit is crucial.

CONCLUSION(S)

In summary, this patient presented with hypoglycaemia, ketonuria, hyperammonaemia, and metabolic acidosis, leading to a diagnosis of profound biotinidase deficiency due to a novel nonsense homozygous mutation in the BTD gene. This rare case highlights that profound biotinidase deficiency can be an uncommon cause of early neonatal deterioration. The novel mutation described here has not been previously documented. Unlike other inborn errors of metabolism, biotinidase deficiency can be effectively treated with lifelong biotin supplementation.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Dec 12, 2024
- Manual Googling: Mar 20, 2025
- iThenticate Software: Apr 19, 2025 (5%)

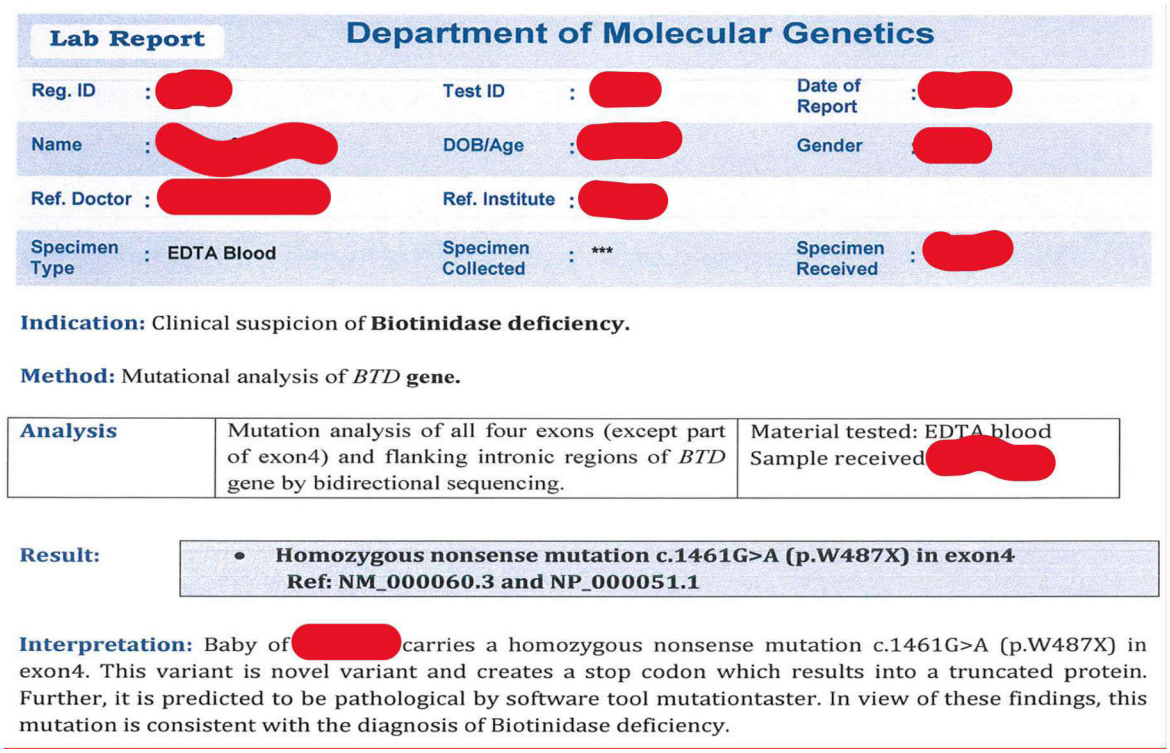
ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Dec 11, 2024**
Date of Peer Review: **Feb 13, 2025**
Date of Acceptance: **Apr 22, 2025**
Date of Publishing: **Oct 01, 2025**

Scanned copy of the Genetic report:



Lab Report — **Department of Molecular Genetics**

Reg. ID	: [redacted]	Test ID	: [redacted]	Date of Report	: [redacted]
Name	: [redacted]	DOB/Age	: [redacted]	Gender	: [redacted]
Ref. Doctor	: [redacted]	Ref. Institute	: [redacted]		
Specimen Type	: EDTA Blood	Specimen Collected	: ***	Specimen Received	: [redacted]

Indication: Clinical suspicion of **Biotinidase deficiency.**

Method: Mutational analysis of *BTD* **gene.**

Analysis	Mutation analysis of all four exons (except part of exon4) and flanking intronic regions of *BTD* gene by bidirectional sequencing.	Material tested: EDTA blood Sample received [redacted]

Result:
- **Homozygous nonsense mutation c.1461G>A (p.W487X) in exon4**
  Ref: NM_000060.3 and NP_000051.1

Interpretation: Baby of [redacted] carries a homozygous nonsense mutation c.1461G>A (p.W487X) in exon4. This variant is novel variant and creates a stop codon which results into a truncated protein. Further, it is predicted to be pathological by software tool mutationtaster. In view of these findings, this mutation is consistent with the diagnosis of Biotinidase deficiency.