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Case Report

Neonatal metabolic crisis: a case report of HMG-CoA lyase deficiency

Amrutha Nandini Ratnapu[1]*, Venkataramana Reddy[2], Chapay Soren[2], M. Geethika[3], K. Puja Devi[2]

[1]SVS Medical College, Mahabubnagar, Telangana, India
[2]Department of Pediatrics, SVS Medical College, Mahabubnagar, Telangana, India
[3]Department of Radiology, SVS Medical College, Mahabubnagar, Telangana, India

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***Correspondence:**
Dr. Amrutha Nandini Ratnapu,
E-mail: amruthanandiniratnapu@gmail.com

ABSTRACT

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) lyase deficiency is a rare autosomal recessive metabolic disorder characterized by impaired ketogenesis and leucine catabolism, leading to nonketotic hypoglycemia, hyperammonemia, and metabolic acidosis. We present a case of a three-day-old male neonate who exhibited poor feeding, lethargy, and respiratory distress, progressing to clonic seizures and severe metabolic decompensation. Initial laboratory findings revealed hypoglycemia, hyperlactatemia, hyperammonemia, and metabolic acidosis with absent ketones. A comprehensive metabolic workup, including urinary organic acid analysis and tandem mass spectrometry, confirmed the diagnosis of HMG-CoA lyase deficiency. The neonate was managed with intravenous dextrose, sodium bicarbonate, and L-carnitine supplementation, leading to gradual clinical improvement. This case highlights the importance of early recognition and prompt management of inborn errors of metabolism, particularly in neonates presenting with acute metabolic crises. The report underscores the need for comprehensive newborn screening to facilitate early diagnosis and prevent life-threatening complications.

Keywords: HMG-CoA lyase deficiency, Neonatal metabolic crisis, Nonketotic hypoglycemia, Hyperammonemia, Metabolic acidosis, Neonatal seizures

INTRODUCTION

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) lyase deficiency is a rare autosomal recessive disorder of ketogenesis and leucine catabolism, first described by Faull in 1976.[1] This disorder results from mutations in the HMGCL gene, leading to the accumulation of toxic intermediates in the leucine degradation pathway and impaired production of ketone bodies. The estimated prevalence of HMG-CoA lyase deficiency is fewer than 1 in 100,000 live births, though this may be an underestimation due to misdiagnosis or underreporting.[2] A recent systematic review identified 211 reported cases, with an overall mortality rate of 16%.[3] The clinical presentation of HMG-CoA lyase deficiency typically occurs in the neonatal period or early infancy, often triggered by fasting, infection, or excessive physical exertion. Affected individuals present with acute metabolic decompensation, characterized by hypoketotic hypoglycemia, metabolic acidosis, hyperammonemia, and hyperlactatemia. These metabolic disturbances can lead to severe complications, including seizures, lethargy, coma, and even death if not promptly managed. The absence of ketone bodies during hypoglycemia is a hallmark of this condition, as the body is unable to utilize ketones as an alternative energy source.

Despite the severity of the initial presentation, early diagnosis and appropriate management can lead to favorable long-term outcomes. However, the nonspecific nature of the symptoms often leads to delayed diagnosis or misdiagnosis, particularly in settings where metabolic screening is not routinely performed. This case report describes a neonate with HMG-CoA lyase deficiency

who presented with acute metabolic decompensation, highlighting the challenges in diagnosis and the importance of early intervention. The report also emphasizes the role of comprehensive metabolic workup and dietary management in improving outcomes for patients with this rare disorder.

CASE REPORT

A three-day-old male neonate was admitted to the NICU with a day history of poor feeding, decreased activity, and increased work of breathing. The child was a late preterm born at 36 weeks of gestation to a primi mother with 2nd-degree consanguinity via elective cesarean section (LSCS). APGAR score was not recorded. However, the mother denied any delay in crying. Regular antenatal checkups were conducted, with a maternal history of fever lasting 10 days during the third month of pregnancy, for which she received oral antibiotics.

There was no history of urinary symptoms, abnormal vaginal discharge, prolonged rupture of membranes, or foul-smelling amniotic fluid. Supplementations were received as per the guidelines. The child was exclusively breastfed immediately after the delivery. The neonatal anthropometry included a weight of 2.8 kg, a length of 46 cm, and a head circumference of 33 cm. For the first three days of life, he was alert, active, and breastfeeding well. At the end of the third day, the mother noticed a gradual decline in activity, followed by poor feeding, and lethargy associated with an increased respiratory effort.

These observations led to the infant's immediate admission to the NICU for further evaluation and management. On the day of admission, the baby developed clonic seizures with low blood glucose. Family history revealed an unexplained death of a previous sibling at 7 months of age, who presented with respiratory distress.

Clinical examination

Upon examination, the neonate exhibited a weak cry, poor sucking, reduced activity, signs of dehydration, and a flat anterior fontanelle. The Moro reflex was bilaterally symmetrical but incomplete, and no obvious external congenital anomalies were noted. The Silverman-Anderson respiratory severity score was 4, indicating moderate respiratory distress.

A comprehensive set of investigations were performed to assess possible metabolic, infectious, and endocrine causes. Routine laboratory tests, including hemogram, serum electrolytes, arterial blood gas analysis, and chest X-ray, were conducted. Sepsis screening included C-reactive protein, procalcitonin, and cultures of blood, urine, and cerebrospinal fluid (CSF). A metabolic workup was initiated, evaluating serum glucose, ketones, lactate, ammonia, and urine ketones. Additionally, endocrine assessments, including serum insulin, cortisol, and thyroid function tests, were performed. Given the presence of seizures and hypotonia, the neonate was intubated and administered anti-seizure medication. During the course of illness, he developed coagulopathy, necessitating platelet transfusion and vitamin K administration. Metabolic abnormalities, including hypoglycemia and acidosis, were managed with intravenous 10% dextrose and sodium bicarbonate. Considering the possibility of vitamin-responsive inborn errors of metabolism, the infant was also resuscitated with thiamine and biotin.

Laboratory findings revealed hypoglycemia, elevated lactate (40.2 mg/dl), hyperammonemia (222 µg/dl), metabolic acidosis (pH 7.15) with increased anion gap (16 mEq/l), and absent serum and urine ketones. Coagulation abnormalities included prolonged PT (37.5 seconds; control: 13.5 seconds), elevated INR (5.09), and increased D-dimer (1520 µg/l), as shown in table 1 below. Mild transaminitis was noted (AST: 52 IU/l, ALT: 39 IU/l, reference range: 10–37 IU/l). Considering possible intrauterine infection, pneumonia, meningitis, or sepsis, a comprehensive infectious disease workup, including blood, urine, and CSF cultures, were performed and found to be negative. Neuroimaging findings showed no evidence of meningitis.

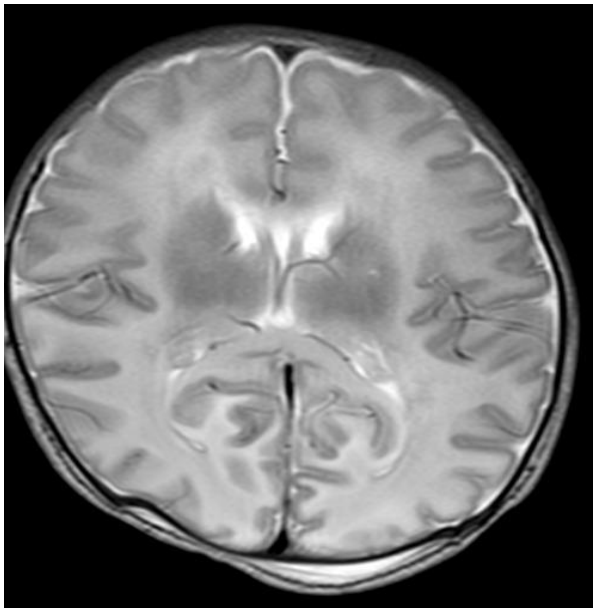

Figure 1: T2 axial, on day 11, showing bilateral occipital lobe and splenium of corpus callosum hyperintensity.

Differential diagnosis

Based on the preliminary history and laboratory findings, a metabolic disorder was strongly suspected, given the presence of high anion gap metabolic acidosis, hyperammonemia and hyperlactatemia, and hypoglycemia with absent ketone bodies. These findings were indicative of acylcarnitine-related conditions, such

as fatty acid oxidation disorders and organic acidemias, with mitochondrial disorders also considered in the differential diagnosis. The initial symptom-free period, followed by hypotonia, poor feeding, respiratory distress, hypoglycemia, and clonic seizures, in conjunction with metabolic findings, strongly suggested an inborn error of metabolism.

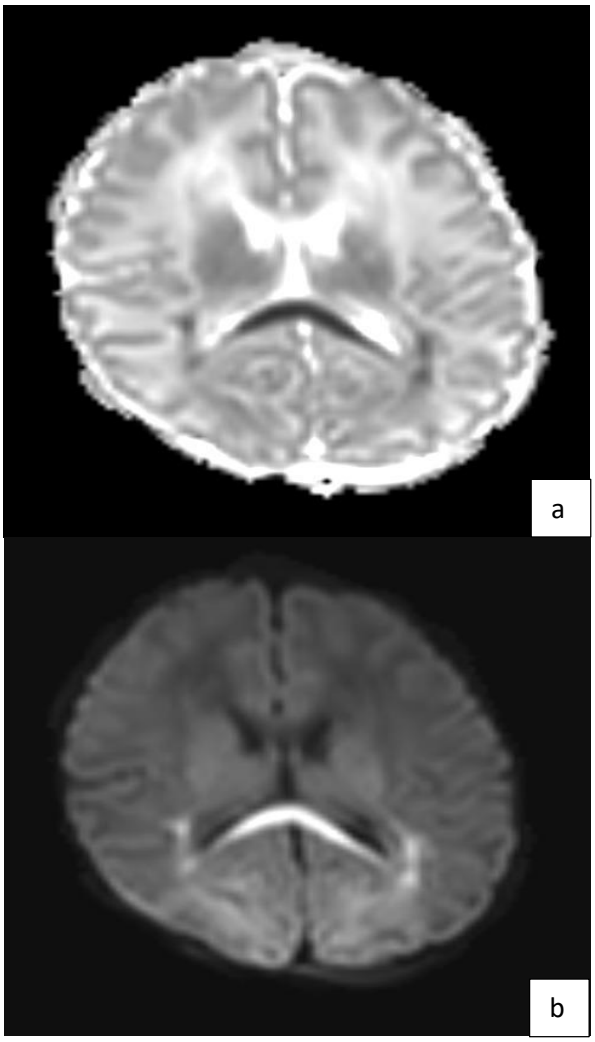

Figure 2 (a and b): DWI and ADC axial images, respectively, showing diffusion restriction in splenium and bilateral occipital lobes.

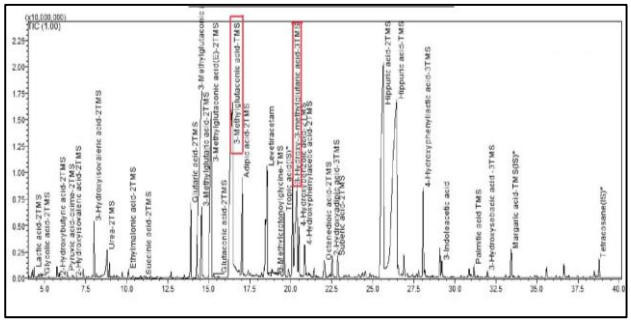

Figure 3: Urinary organic acid (gas chromatography-mass spectrometry) of the patient.

The newborn demonstrated gradual clinical improvement, with metabolic derangements resolving by day 5. His vital signs stabilized, euglycemia was maintained, and no further seizures were observed. The infant was successfully extubated on day 4 and transitioned to non-invasive respiratory support for an additional day before being weaned off completely.

MRI of brain was performed on day 11, revealing excessive T2 hyperintensity in the bilateral parieto-occipital regions, splenium of the corpus callosum, bilateral thalami, posterior limb of the internal capsule, and deep white matter of the corona radiata. Diffusion-weighted imaging (DWI) showed restricted diffusion with reversal on apparent diffusion coefficient (ADC) maps, indicative of cytotoxic edema and hypoglycemic injury, as demonstrated in the accompanying image. Feeding was initiated on day 4 of the illness. Due to financial constraints, a mixed diet comprising breast milk and a leucine-free formula was introduced. The infant tolerated feeds well without any further episodes of metabolic decompensation.

Biochemical investigations confirmed the diagnosis. The urinary organic acid profile, as shown in figure 2, revealed mild to significant elevation of 3-hydroxy-3-methylglutaric acid, 3-methylcrotonylglycine, 3-methylglutaconic acid, 3-methylglutaric acid, 2-hydroxybutyric acid, and 2-hydroxyisovaleric acid. Tandem mass spectrometry (TMS) showed elevated C5OH, consistent with HMG-CoA lyase deficiency. Notably, amino acid levels were within the normal range.

Table 1: Daily blood workup.

Parameter	Day1	Day 2	Day 3	Day 4	Day 5
pH	7.15	7.49	7.32	7.49	7.47
HCO_3^-(mEq/l)	11.0	12.6	13.5	15	17.4
Ammonia (µg/dl)	222	186	140	110	96
Lactate plasma (mg/dl)	40.2	194	100	46	18
INR	5.09	3.6	3.1	2.4	1.3

DISCUSSION

HMG-CoA lyase deficiency (HMGCLD) is a rare autosomal recessive metabolic disorder that typically presents as an acute metabolic crisis in the early neonatal period. Approximately 60–70% of cases occur within the first year of life, with around 30% manifesting between the second and fifth day of life. The incidence is estimated to be less than 1 in 100,000 live births. Although the clinical presentation is highly heterogeneous, symptoms usually emerge in the neonatal period or early infancy, often with life-threatening metabolic decompensation if not promptly managed. Late-onset cases beyond infancy are rare, and despite the

severity of the initial presentation, most patients achieve a favourable long-term outcome with normal cognitive development.[2,4]

During hypoglycemia, the body compensates by producing ketone bodies as an alternative energy source. However, in HMGCL deficiency, this compensatory mechanism is impaired due to defective ketogenesis, leading to a nonketotic hypoglycemic state. Since HMG-CoA lyase also plays a crucial role in leucine catabolism, its deficiency results in accumulation of leucine and its toxic metabolites, preventing their conversion into essential downstream products, such as acetoacetate and acetyl-CoA, which are critical for energy production.

This leads to a build-up of toxic intermediates, including 3-methylglutaconyl-CoA (3-MGC), 3-methylglutaconate (3-MGL), and 3-hydroxyisovalerate (3-HIVA). The combination of ketone body deficiency and toxic metabolite accumulation severely disrupts metabolic homeostasis, leading to secondary metabolic dysfunction, and in severe cases, acute encephalopathy. Due to its impact on fatty acid metabolism and organic acid accumulation, HMGCL deficiency is classified as both a fatty acid oxidation disorder and an organic aciduria.[3,5]

Despite this metabolic imbalance, amino acid levels were found to be normal in our case. Symptoms typically emerge following fasting, infection, increased dietary protein intake, or the stress of birth. Affected individuals frequently present with acute metabolic decompensation, characterized by hypoketotic hypoglycemia, metabolic acidosis, vomiting, dehydration, hypotonia, and lethargy. The combination of nonketotic hypoglycemia, hyperammonemia, and hyperlactatemia strongly suggests an inborn error of metabolism.

However, due to its rare incidence and nonspecific clinical presentation, the diagnosis of HMG-CoA lyase deficiency is often delayed or misdiagnosed. In our case, the neonate was initially treated for sepsis, given risk factors such as preterm LSCS delivery, low birth weight, respiratory distress, and hypotonia, before further metabolic investigations identified the underlying disorder.[6,2]

Although there are no standardized guidelines for dietary management, evidence from previous case studies suggests that a leucine-, protein-, and fat-restricted diet can improve prognosis.[3,4] The mother was counseled to follow dietary modifications, particularly during illness, when the body enters a catabolic state, leading to increased protein breakdown and additional strain on the liver. Frequent feeding was recommended to prevent fasting-induced metabolic crises, along with nocturnal cornstarch supplementation to provide a sustained energy source. Additionally, elevated C5OH (3-hydroxyisovalerylcarnitine) indicated secondary carnitine deficiency, which occurs due to organic acid conjugation with free carnitine, leading to carnitine depletion and impaired fatty acid oxidation. To counteract this, the neonate was supplemented with L-carnitine to restore metabolic balance.[4]

CONCLUSION

This case underscores the necessity of considering inborn errors of metabolism, such as HMG-CoA lyase deficiency, even when amino acid levels appear normal. It highlights the crucial role of comprehensive newborn screening in the early identification and management of metabolic disorders to prevent life-threatening complications.

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