

Case Report

## Thiamine-Responsive Maple Syrup Urine Disease in an Infant: A Rare Inborn Error of Branched-Chain Amino Acid Metabolism

### *Bir Bebekte Tiamine Yanıtlı Akçağaç Şurubu İdrar Hastalığı: Dallı Zincirli Amino Asit Metabolizmasının Nadir Bir Doğuştan Hatası*

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#### ABSTRACT

**Background:** Maple syrup urine disease (MSUD) is a rare autosomal recessive inborn error of metabolism caused by deficient activity of the branched-chain  $\alpha$ -ketoacid dehydrogenase (BCKD) complex.

**Case Presentation:** We report the case of a 3-month-old male infant, born to a non-consanguineous couple, who presented with two episodes of seizures characterized by upward rolling of the eyes, each lasting approximately three minutes. The child also exhibited tachypnea, irritability, vomiting and poor feeding for 20 days. Exome sequencing revealed a homozygous missense variant in exon 3 of the *BCKDHB* gene (c.832G>A; p.Gly278Ser). The clinical and genetic findings were consistent with thiamine-responsive maple syrup urine disease. Management focused on high-dose thiamine supplementation, dietary branched-chain amino acid restriction, antiepileptic therapy, and supportive care. The infant showed marked clinical improvement and was discharged in stable condition with plans for close follow-up.

**Conclusion:** This case underscores the importance of considering thiamine-responsive MSUD in infants presenting with early-onset neurological symptoms and feeding difficulties. Early genetic diagnosis and targeted metabolic therapy, particularly thiamine supplementation, can lead to rapid clinical stabilization and may reduce the risk of recurrent metabolic decompensation and long-term neurodevelopmental impairment.

**Keywords:** maple syrup urine disease, autosomal recessive inheritance, homozygous missense variation, poor feeding, convulsions

#### ÖZET

**Arka Plan:** Akçağaç şurubu idrar hastalığı (MSUD), dallı zincirli  $\alpha$ -ketoasit dehidrogenaz (BCKD) kompleksinin yetersiz aktivitesinden kaynaklanan nadir bir otozomal resesif doğuştan metabolizma hatasıdır.

**Olgu Sunumu:** Akraba olmayan bir çiftten doğan, gözlerin yukarı kayması ile karakterize, her biri yaklaşık üç dakika süren iki nöbet epizoduyla başvuran 3 aylık bir erkek bebek olgusunu sunuyoruz. Çocukta ayrıca taşipne, irritabilite, kusma ve 20 gündür süren beslenme güçlüğü mevcuttu. Ekzom dizileme, *BCKDHB* geninin 3. ekzonunda homozigot bir missense varyant (c.832G>A; p.Gly278Ser) ortaya koydu. Klinik ve genetik bulgular tiamine yanıtı akçağaç şurubu idrar hastalığı ile uyumluydu. Tedavi, yüksek doz tiamine takviyesi, diyetle dallı

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zincirli amino asit kısıtlaması, antiepileptik tedavi ve destekleyici bakıma odaklanmıştır. Bebeğe belirgin klinik iyileşme gözlenmiş ve yakın takip planıyla stabil durumda taburcu edilmiştir.

**Sonuç:** Bu olgu, erken başlangıçlı nörolojik semptomlar ve beslenme güçlüğü ile başvuran bebeklerde tiamine yanıtı MSUD'nin göz önünde bulundurulmasının önemini vurgulamaktadır. Erken genetik tanı ve hedefe yönelik metabolik tedavi, özellikle tiamine takviyesi, hızlı klinik stabilizasyona yol açabilir ve tekrarlayan metabolik dekompansementasyon ile uzun dönemli nörogelişimsel bozukluk riskini azaltabilir.

**Keywords:** *akçaağaç şurubu idrar hastalığı, otozomal resesif kalıtım, homozigot missense varyasyon, beslenme güçlüğü, konvülsiyon*

## INTRODUCTION

Maple syrup urine disease (MSUD) is an autosomal recessive metabolic disorder characterized by impaired activity of the branched-chain  $\alpha$ -ketoacid dehydrogenase (BCKAD) complex, which catalyzes the second step in the catabolic pathway of the branched-chain amino acids (BCAAs), namely leucine, isoleucine, and valine.(1)

MSUD occurs worldwide, with an estimated incidence of approximately 1 in 185,000 live births.(1) Based on residual BCKAD enzymatic activity and clinical presentation, MSUD is commonly classified into five phenotypic forms: classic, intermediate, intermittent, thiamine-responsive, and E3 (dihydrolipoamide dehydrogenase) deficiency.(2) Thiamine-responsive MSUD is a rare subtype associated with pathogenic variants in the DBT (Dihydrolipoamide Branched-Chain Transacylase) gene, which encodes the E2 subunit of the BCKAD complex, or the BCKDHB (Branched-Chain Ketoacid Dehydrogenase E1 Subunit Beta) gene, which encodes the E1 $\beta$  subunit.(1)

The disorder is more prevalent in populations with a high rate of consanguinity. Three genes-BCKDHA (Branched-Chain Ketoacid Dehydrogenase E1 Subunit Alpha), BCKDHB (Branched-Chain Ketoacid Dehydrogenase E1 Subunit Beta), and DBT (Dihydrolipoamide Branched-Chain Transacylase)-are primarily involved in the metabolism of branched-chain amino acids. Under normal conditions, individuals possess two functional copies of each of these genes. In patients with MSUD, bi-allelic pathogenic variants in one of these genes lead to deficient enzymatic activity, resulting in impaired breakdown of BCAAs. Consequently, toxic metabolites accumulate, giving rise to the characteristic clinical manifestations.(3)

Clinical symptoms typically appear shortly after birth and include poor appetite, feeding difficulties, vomiting, weak suck, weight loss, a high-pitched cry, irritability, and a characteristic sweet odour of the urine.(3) The diagnosis of MSUD is based on a

combination of clinical findings and biochemical and molecular investigations. Biochemical features include elevated plasma concentrations of BCAAs, particularly leucine and isoleucine, as well as increased levels of branched-chain  $\alpha$ -hydroxy acids and branched-chain  $\alpha$ -ketoacids (BCKAs) in urine.

Management of MSUD primarily involves dietary restriction of leucine with careful and regular monitoring of plasma amino acid levels. Infants are initially managed with specialized MSUD formulas.(3) In severe cases, extracorporeal therapies such as dialysis or plasma exchange may be required to rapidly reduce toxic metabolite levels. Thiamine supplementation serves as an important adjunctive therapy, particularly in thiamine-responsive MSUD, where residual BCKAD activity allows for improved dietary BCAA tolerance following supplementation.(2) In selected patients with severe or poorly controlled disease, liver transplantation is considered an effective therapeutic option, as the enzymes involved in BCAA metabolism are predominantly expressed in the liver.(3)

## CASE REPORT

A 3-month-old male infant, born to a non-consanguineous couple, was brought to the emergency department with acute-onset seizures and respiratory distress. According to the parents, the child had experienced two seizure episodes characterized by upward rolling of the eyes, each lasting approximately three minutes, which resolved following administration of antiepileptic medication. There were no associated abnormal limb movements or oral frothing. On the day of admission, the infant developed tachypnea, had been unusually irritable and inconsolable since the preceding night.

The parents also reported a history of recurrent vomiting for approximately 20 days prior to admission. The vomiting was non-projectile, milk-containing, and curd-like in nature. Although vomiting had subsided three days before presentation, the infant continued to

exhibit poor feeding. There was no history of fever, diarrhea, trauma, or drug intake.

The infant was born at term via normal vaginal delivery with a birth weight of 3.4 kg. The neonatal period was uneventful. Growth and developmental milestones were appropriate for age, and immunizations had been administered up to 1.5 months. There was no significant past medical history or family history of neurological or metabolic disorders.

On arrival, the infant was noted to have oxygen desaturation with peripheral cyanosis and an abnormal respiratory pattern. In view of impending respiratory failure, endotracheal intubation and mechanical ventilation were initiated. Following stabilization, the infant weighed 4.8 kg, and vital parameters were within normal limits. Respiratory system examination revealed bilateral equal air entry without added sounds, with a respiratory rate of 68 breaths per minute.

Initial laboratory investigations revealed significant hyponatremia (123.9 mmol/L) with mild hypochloremia (94.5 mmol/L). Serum lactate was markedly elevated at 10.6 mmol/L. Arterial blood gas analysis demonstrated a high anion gap metabolic acidosis with a compensatory respiratory alkalosis. Given the presence of seizures, metabolic acidosis, and elevated lactate in a previously healthy infant, an inborn error of metabolism was suspected.

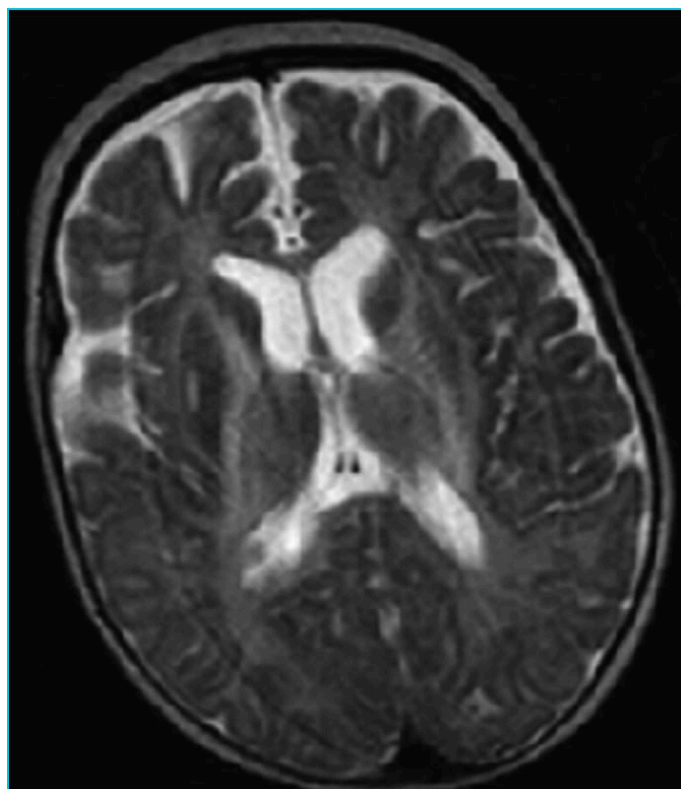
Plasma amino acid analysis showed markedly elevated levels of branched-chain amino acids, including leucine(300-1200  $\mu$ mol/L), isoleucine(150-600  $\mu$ mol/L), and valine(300-900  $\mu$ mol/L). Magnetic resonance imaging (MRI) of the brain demonstrated bilateral symmetrical T2-weighted hyperintensities involving the basal ganglia, along with features of intramyelinic edema, findings consistent with metabolic encephalopathy (Figure 1).

Genetic test Clinical exome sequencing revealed a homozygous missense variant in exon 3 of the *BCKDHB*

gene (c.832G>A; p.Gly278Ser).

This variant has previously been reported in association with thiamine-responsive forms of maple syrup urine disease and is known to have a very low allele frequency. Based on the clinical presentation, biochemical abnormalities, characteristic neuroimaging findings, and genetic confirmation, a diagnosis of thiamine-responsive maple syrup urine disease was established.

The infant was treated with antiepileptic therapy using levetiracetam syrup (0.7 ml BD) and was initiated on Tab.thiamine supplementation(100 mg OD) through oral route (Diluted in 10 ml of sterile water from which 1 ml was given) in view of the thiamine-responsive phenotype. Supportive management included intravenous fluids, correction of electrolyte imbalance with 3% hypertonic saline, and multivitamin supplementation. Empirical intravenous antibiotics like ceftriaxone(200 mg BD) were administered, along with proton pump inhibitors like Pantoprazole (5 mg OD) , antiemetics like Ondansetron (0.3ml SOS, and prokinetic agents( Domperidone 1.5 mg QID) . Exclusive breastfeeding until 6 months of age was advised and the baby was given a special BCAA-free,lactogen free MSUD formula (Mix 2 spoons in warm water, make a fine paste and feed it to the baby) as the top feed. This helps prevent the accumulation of harmful amino acids. Small, controlled supplementation of valine and isoleucine is done to support normal growth. Adequate calorie intake is maintained to avoid protein breakdown, and tab.thiamine supplementation(100 mg OD) through oral route (Diluted in 10 ml of sterile water from which 1 ml was given) to improve metabolic function in thiamine-responsive MSUD. The parents were counseled extensively regarding dietary modification, long-term metabolic management, and the importance of adherence to thiamine supplementation and follow-up.



**Figure 1.** T2-weighted image reveals hyperintense changes in the pyramidal tract and extreme capsule.

## DISCUSSION

Maple syrup urine disease (MSUD) is a rare autosomal recessive disorder of branched-chain amino acid metabolism, with an estimated global incidence of approximately 1 in 185,000 live births.(1) While the classic form typically presents in the neonatal period, variant phenotypes—including thiamine-responsive MSUD (TR-MSUD)—may manifest later in infancy with variable and often nonspecific clinical features, which can contribute to diagnostic delay.

The present case highlights several clinically important aspects of TR-MSUD. Our patient presented at three months of age with seizures, irritability, feeding difficulties, metabolic acidosis, and respiratory distress. These manifestations overlap with the neurological features described in previous pediatric reports, including lethargy and seizures, as documented by Cheng et al.(4) However, the relatively delayed onset and the preceding history of prolonged vomiting emphasize the diagnostic challenges posed by variant forms of MSUD, particularly in settings where universal newborn screening is not routinely available.

From a biochemical perspective, the patient demonstrated markedly elevated plasma

concentrations of leucine, isoleucine, and valine, along with severe lactic acidosis. Similar biochemical profiles have been described by Li et al.,(5) who also reported characteristic neuroimaging findings in MSUD. In our case, brain magnetic resonance imaging (MRI) revealed bilateral symmetrical T2-weighted hyperintensities involving the basal ganglia with evidence of intramyelinic edema. These findings are well recognized in MSUD and reflect the susceptibility of myelinated brain structures to the toxic accumulation of branched-chain amino acids and their corresponding ketoacids.(5) The concordance between biochemical abnormalities and neuroimaging findings significantly strengthened the clinical suspicion of an inborn error of metabolism.

Genetic analysis identified a homozygous missense variant in the *BCKDHB* gene (c.832G>A; p.Gly278Ser), a variant previously associated with thiamine-responsive phenotypes. The identification of thiamine responsiveness is clinically significant because of its direct therapeutic implications. As demonstrated in earlier studies by Fernhoff et al.,(6) a subset of patients with MSUD exhibit biochemical and clinical improvement following pharmacological doses of thiamine, attributable to residual activity of the branched-chain  $\alpha$ -ketoacid dehydrogenase complex. Early recognition of this subtype allows for timely initiation of thiamine supplementation, which may improve metabolic stability and neurological outcomes.

The management of our patient—including high-dose thiamine supplementation, dietary restriction of branched-chain amino acids, seizure control, and supportive care—was consistent with previously reported treatment strategies.(1,6) This case further underscores the importance of maintaining a high index of suspicion for metabolic disorders in infants presenting with unexplained seizures, metabolic acidosis, and feeding intolerance. Prompt metabolic evaluation combined with targeted genetic testing is essential for establishing an early diagnosis and enabling individualized therapy, thereby reducing the risk of recurrent metabolic decompensation and long-term neurological sequelae.

## CONCLUSION

This case underscores the importance of considering thiamine-responsive maple syrup urine disease as a potentially treatable variant in infants

presenting with recurrent metabolic decompensation and neurological symptoms. Early biochemical evaluation and genetic testing enabled timely diagnosis and initiation of targeted therapy with high-dose thiamine in conjunction with dietary modification. The rapid clinical and biochemical improvement observed highlights the critical role of prompt intervention in preventing irreversible neurodevelopmental impairment. This report contributes to the limited existing literature on thiamine-responsive MSUD and emphasizes the need for heightened clinical awareness to facilitate early recognition and reduce long-term morbidity.

#### **Patient Consent Form / Hasta Onam Formu**

The parents' of this patient consent was obtained for this study.

#### **Conflict of Interest / Çıkar Çatışması**

The authors declared no conflicts of interest with respect to authorship and/or publication of the article.

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#### **Author Contributions / Yazar Katkıları**

Concept: TD; design: TD,MNA; materials: TD,MNA; data collection and/or processing: TD,MNA; analysis and interpretation: TD,SN,MNA; literature review: SN; writing manuscript: TD,SN,MNA; critical reviews: TD,SN,MNA. All authors participated in the discussion of the case, approved the final version of the manuscript, and agreed to be accountable for the accuracy and integrity of the work.

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