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Case Report

A Classic Case of Maple Syrup Urine Disease and a Novel Mutation in the *BCKDHA* Gene

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ABSTRACT

***Background*:** Maple syrup urine disease (MSUD) is an inherited branched-chain amino acid metabolic disorder caused by the deficiency in the branched-chain alpha-keto acid dehydrogenase (BCKD) complex. In MSUD, elevation of the branched-chain amino acids, such as alpha-keto acid and alpha-hydroxy acid, occurs due to the *BCKDC* gene deficiency, appearing in the blood, urine, and cerebrospinal fluid, which leads to neurological damage and mental retardation. MSUD phenotypically penetrates due to the mutations in the coding genes of four subunits of the BCKD complex, including the *BCKDHA*, *BCKDHB*, *DBT*, and *DLD* genes.

Case report: We aimed to report the cases of three families whose children were affected by MSUD and presented with symptomatic features during the first week of birth, which were identified by mass spectrometry. DNA study was performed as a diagnosis panel containing four encoded *BCKDC* subunit genes.

Conclusion: In the current study, DNA analysis and phenotypic manifestations indicated a novel mutation of c.143delT, p.L48Rfs*15 in the BCKDHA gene in a homozygous state, which is a causative mutation for the classic MSUD phenotype. Early diagnosis and neonatal screening are recommended for the accurate and effective treatment of this disease.

Keywords: BCKD deficiency, DNA mutational analysis, Maple syrup urine disease

Introduction

Maple syrup urine disease (MSUD) is an inherited branched-chain amino acid (BCAA) metabolic disorder, which is caused by the deficiency of the branched-chain alpha-keto acid dehydrogenase complex (BCKDC). Six subunits are responsible for the breakdown of the leucine, isoleucine, and valine amino acids (1). Incidence of MSUD is estimated to be 1:185,000 among infants worldwide (2, 3), while in the Old Order Mennonite groups, the incidence was 1:380.

Branched-chain amino acids, such as alpha-keto acid and alpha-hydroxy acids, accumulate due to the BCKDC deficiency in the blood, urine, and cerebrospinal fluid, giving rise to neurological damage and mental retardation. Neonatal screening tests are beneficial in the early diagnosis of MSUD, as well as the control and treatment of the disease (4).

BCKDC subunits E1α, E1β, E2, and E3 are encoded by the *BCKDHA* gene on chromosome 19q13.1, *BCKDHB* gene on chromosome 6p21-22, *DBT* gene on chromosome 1p21-31, and *DLD* gene on chromosome 7q31-32, respectively (5). Various types of MSUD are classified based on the symptom manifestation, age at onset, and genetic causes. The most prevalent neonatal form of the disease is classic, severe MSUD. Some other forms of the disease include intermediate MSUD, intermittent MSUD, thiamine-responsive MSUD, and E3-deficient MSUD with lactic acidosis (6).

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In this paper, we aimed to report the cases of three separate families whose children were affected by MSUD. DNA analysis results and phenotypic presentations were documented, and a novel mutation was observed. In addition, a brief review of the clinical and genetic characteristics of the previous cases has been provided.

Case report

Three neonates were diagnosed with MSUD in Namazi Hospital in Shiraz, Iran by mass spectrometry. All the three patients presented with symptomatic clinical features within 3-7 days after birth. Some indications of the neurological symptoms included lethargy, poor feeding, convulsion, dystonia, and coma. Brain computed tomography (CT) scan was performed, revealing brain edema and signs of increased intracranial pressure. The neonates were provided with a low-protein special formula.

DNA study was performed based on the polymerase chain reaction (PCR) amplification and direct sequencing of all the coding exons and flanking intronic sequences of the *BCKDHA*, *BCKDHB*, *DBT*, and *DLD* genes. These procedures were carried out in collaboration with the Center for Human Genetics (Freiburg, Germany), supported by Shiraz University of Medical Sciences (Shiraz, Iran) in 2012.

In the first family, a five-year-old boy presented with the clinical indications of classic MSUD during the first week of birth. As the first-degree relatives of the neonate, the parents had no history of MSUD. Mutation was identified in c.117delC, p.R40Gfs*23 in the *BCKDHA* gene in a homozygous state, while no mutation was observed within the other genes.

In the second family, a five-year-old boy presented with the clinical features of classic MSUD during the first week of birth. As the first-degree relatives of the neonate, the parents had a history of losing a child due to MSUD. DNA study showed mutation in c.508C>T, p.R170C in the *BCKDHB* gene in a homozygous state, which has been described as a causative mutation for MSUD in a parallel research (7).

In the third family, a five-year-old girl presented with the clinical indications of classic MSUD during the first week of birth. As the first-degree relatives of the neonate, the parents had no history of MSUD. DNA analysis was indicative of mutation in c.143delT, p.L48Rfs*15 in the *BCKDHA* gene in a homozygous state, which has been described as a causative mutation for MSUD.

Of note, written informed consent was obtained from the parents prior to the submission of this report.

Discussion

Classic, severe form of MSUD was first described in 1954 as a familial syndrome occurring within the first week of birth in four siblings who had progressive infantile cerebral dysfunction associated with an unusual urinary substance with maple syrup odor (8). Biochemical signs of this form of MSUD include elevated BCAAs and allo-isoleucine in the plasma, increased branched-chain hydroxy acids and keto acids in the urine, positive urine dinitrophenylhydrazine test, and ketonuria. Furthermore, BCKD enzyme activity in this form of the disease is less than 2%. Classic MSUD might be unnoticed in neonatal screening due to the slow rise of blood leucine levels (9, 10).

Individuals with the same MSUD genotype and penetrance may exhibit various clinical indications, and no strict genotype-phenotype correlation has been defined for MSUD. Moreover, severity of the phenotype is relative to the residual BCKAD enzyme activity, illness, dietary regimen, and catabolic stress (11).

The third patient described in this report was diagnosed with classic MSUD and had a novel homozygous mutation in c.143delT, p.L48Rfs*15 in the *BCKDHA* gene, which has not yet been described as a causative mutation for MSUD. This mutation causes a frame shift and preterminal stop codon and is expected to lead to loss of function by nonsense-mediated mRNA decay; therefore, it may be considered pathogenic.

Other deletions in the *BCKDHA* gene have been shown to be causative for MSUD, while one base pair deletion in c.117delC has been reported in classic MSUD (12). Additionally, approximately 45% of the MSUD mutations are reported in the *BCKDHA* gene, which are known as sequence variants and deletions (2).

Conclusion

In conclusion, early diagnosis and neonatal screening should be considered for the accurate and effective treatment of MSUD in newborns. Furthermore, protein structure and activity analysis of the BCKD enzyme in the presence of novel mutations is recommended to justify the clinical manifestations of MSUD patients.

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Conflicts of interests

None declared.

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