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Maple Syrup Urine Disease Induced Grand Mal Seizures: A Case Report

*Gautam Satheesh[1], Suja Johnson[1], Balraj Guhan[2], Niyas Ahammed[2]

[1]Department of Pharmacy Practice, National College of Pharmacy, Calicut, Kerala, India. [2]Department of Paediatrics, KMCT Woman and Child Hospital, Calicut, Kerala, India.

Abstract

Background

Maple Syrup Urine Disease (MSUD) is a rare autosomal recessive metabolic error, characterized by Branched Chain α-Keto-acid Dehydrogenase Complex (BCKDC) deficiency. Mutations in 3 genes can lead to abnormal metabolism and accumulation of leucine, isoleucine, valine and corresponding keto-acids. MSUD affects 1 in 185,000 infants globally. Seizure is a common presentation among neonates. However, in intermediate MSUD, seizures have a delayed and insidious onset, along with developmental

Case Report

We report a case of grand mal seizures in a patient with intermediate MSUD, presenting with multiple episodes of seizure, dystonia, spastic quadriplegia, involuntary micturition and oculogyric crisis. Seizures were managed successfully with intravenous lorazepam and other supportive measures. The patient was advised to strictly adhere to branched chain amino acid restricted diet.

Conclusion

This case report emphasizes on the importance of medication adherence and dietary restrictions to prevent permanent psychomotor damage or death.

Key Words: GTCS, Genetic, MSUD, Seizures, Quadriplegia.

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Corresponding Author:

Gautam Satheesh, Department of Pharmacy Practice, National College of Pharmacy, Calicut, Kerala, India. Postal code: 673602.

Email: gautamsatheesh@gmail.com

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1- INTRODUCTION

Maple Syrup Urine Disease (MSUD) is a rare autosomal recessive error in metabolism of amino acids caused by the deficiency of branched-chain alpha-keto acid dehydrogenase complex enzyme system (BCKDC). This enzyme deficiency leads to the abnormal metabolism of branched chain amino acids and subsequent accumulation of leucine, isoleucine and valine as well as their corresponding keto acids in the blood and urine, resulting in the characteristic fruity odour (1). This deficiency can be caused by mutations in three genes which encode the catalytic components of the BCKDC (E1α, E1β, E2, and E3); namely *BCKDHA*, *BCKDHB* and *DBT* genes (**Table.1**). Mutation in E3 component (*DLD* gene) on chromosome 7q31 causes a severe condition termed as MSUD3, the symptoms of which vary from severe neonatal lactic acidosis to liver disorder, and generally subside with age. These homozygous or heterozygous mutations lead to defective oxidative decarboxylation of the branched chain amino acids (1). MSUD is rare in most populations, with incidence estimates of 1 in 185,000 live births globally (2, 3). Five phenotypes of MSUD have been recognized so far; classic, intermediate, intermittent thiamine responsive and MSUD3. Classic phenotype is the most common and most severe phenotype. While seizure is a common presentation in the neonatal stage in classic MSUD, development of seizures is often delayed and insidious in intermediate MSUD. Seizures are mostly generalized or focal; however status epilepticus may develop, requiring immediate intervention (3).

Table-1: Genetic description of MSUD. Note that mutations in E1 and E2 components may result in any of the phenotypes except MSUD 3 which is specific to E3 component.

Gene Involved	Chromosome	Comments	Most Commonly Associated Phenotype
BCKDHA	19q13.1-q13.2	In Mennonite population, asparagine commonly replaced tyrosine at position 438	Severe classic MSUD
BCKDHB	6q14.1	In Ashkenazi population, proline commonly replaced asparagine at position 183	Severe classic MSUD
DBT	1p21.2	>70 mutations identified, frequent in mild variants of the disease (delayed onset of symptoms)	Intermediate and intermittent MSUD
DLD	7q31	Mutation in E3 component i.e. DLD deficiency results in severe neonatal disorder.	MSUD 3

MSUD: Maple Syrup Urine Disease; BCKDC: Branched Chain α-Keto-acid Dehydrogenase Complex; DLD: dihydrolipoyl dehydrogenase.

2- CASE REPORT

A fourteen year old female patient, previously diagnosed with intermediate MSUD, was admitted to a teaching hospital in Kerala, India, with multiple episodes of grand mal and rigidity of upper and lower limbs. Each episode was associated with oculogyric crisis and involuntary micturition. The patient has a history of dystonia of both limbs and spastic quadriplegia. The patient has been undergoing oral Levetiracetam therapy since the age of 5 after the first episode of seizure. The patient is the fifth child of a third degree consanguineous marriage. Two of the patient's elder siblings, a male and a female, died at the ages of 9 months

and 2 years, respectively; of which the female sibling was diagnosed with classic MSUD on post-natal day 8. Neurological examinations revealed dynamic contractures and brisk knee jerks. Routine laboratory investigations were well within normal limits. Developmental evaluation revealed regression of milestones and global developmental delay. The patient was found to have a Grade III stunt. Anthropometric measurement of head circumference revealed microcephaly. The fruity odour characteristic of MSUD was easily observable within the close proximity of the patient. Estimation of plasma proteins showed elevated leucine (946 μmol/L), isoleucine (302 μmol/L), and valine (602 μmol/L). Seizures were managed with anticonvulsants and other supportive measures. Initially, Lorazepam was administered intravenously followed by Fosphenytoin infusion (loading dose of 400 mg in 300 ml normal saline every 30 minutes and then maintained at 50mg). The patient continued to receive Fosphenytoin therapy along with oral Levetiracetam for the entire hospitalization period of 5 days. Supportive measures included normal saline and oxygen administration with nebulization. The patient was advised to strictly adhere to low protein and BCAA restricted diet. Further reviews suggested that the patient's condition has significantly improved without any seizure recurrence following discharge.

3- DISCUSSION

Classic MSUD is the most commonly observed (>80% of cases) and the most severe phenotype, presenting with emesis, seizures and encephalopathy. Classic form develops early (by second week of life). However, in intermediate MSUD, typical signs i.e. developmental delay and seizures develop later. Subjecting an individual with intermediate MSUD to catabolic stress can cause severe leucinosis and even death. Other characteristic findings include ketoacidosis and dystonia (1). Age of onset is a key factor of phenotype determination. The deficiency of BCKDC is responsible for the accumulation of BCAA and their toxic metabolites in blood and urine.

Among the 4 catalytic components of BCKDC (E1α, E1β, E2, and E3), E3 catalytic component serves pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. The underlying mechanism of seizures in MSUD can be explained by accumulation and neurotoxicity of leucine and its transamination product 2-ketoisocaproate. Conversely, accumulation of leucine primarily causes all the neurological manifestations. Elevated plasma levels of isoleucine causes the characteristic odour of MSUD. Interestingly, valine seems to play a very insignificant role in the pathogenesis (4). Proper compliance, appropriate management and strict dietary restrictions are the most important tools to prevent severe complications i.e. status epilepticus, psychomotor retardation and potentially fatal metabolic abnormalities, especially under stressful conditions (5).

Immediate treatment focuses on maintenance of adequate hydration, management of seizures and rapid elimination of BCAA. Peritoneal dialysis or hemodialysis is reserved for critical cases. Permanent damage can be prevented with timely management of manifestations and prevention of extensive ischemia. Prolonged elevation of amino acid levels in the brain during early developmental stages lead to permanent neurological dysfunction. Mental retardation and behavioural abnormalities are common in individuals older than twelve years, warranting use of neuroleptics (6). The patient is obliged to follow the dietary restrictions for the entire lifetime. The diet is essential in normalizing the levels of BCAA in the body, thus preventing developmental or intellectual impairment.

Various synthetic formulas practically devoid of BCAAs have been developed. Avoidance of BCAA rich foods i.e. beef, soy, lentils and diary is beneficial. The risk of development of MSUD is 25% when both the parents are carriers of mutated gene. This risk is significantly higher in consanguineously married individuals. Incidentally, MSUD is more prevalent in countries like Saudi Arabia, India and Lebanon where consanguineous marriage is common [1]. The carrier frequency is 1 in 113 in Ashkenazi Jewish populations. A study conducted in Philippines reported that 1/3rd of MSUD cases were attributable to consanguinity (7).

4- CONCLUSION

Seizures are highly unpredictable in Intermediate MSUD. Failure to receive adequate intervention, often lead to permanent retardation, coma and death. Therefore, adherence to antiepileptic therapy as well as a low protein and BCAA restricted diet is crucial to prevent severe complications. It is also highly essential that the individuals, who are married consanguineously, receive appropriate education about the possible risks of genetic defects they may carry.

5- ABBREVIATIONS

- MSUD: Maple Syrup Urine Disease.
- BCKDC: Branched Chain α-Keto-acid Dehydrogenase Complex.
- DLD: Dihydrolipoamide Dehydrogenase.
- BCAA: Branched Chain Amino Acids.

6- CONFLICT OF INTEREST: None.

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