Abstract: Ten days old girl baby was hospitalized for lethargy and refusal of feeds of one day duration. She is a fourth born child to a second degree consanguineous parents and her elder brother died in neonatal period and the other seven year old brother has developmental delay with seizures. She has one normal male sibling of 3 years age. She was apparently well since birth and was found to be lethargic with shallow breathing, intermittent dystonic posturing and a fruity body odor, on admission. She needed respiratory support and a high rate of glucose infusion to maintain euglycemia. Sepsis work up was negative. Initial evaluation showed increased anion gap metabolic acidosis with increased blood ammonia level. Blood for tandem mass spectrometry, urine for organic acids and blood amino acidogram all showed reports suggestive of Maple syrup urine disease. She improved with special diet devoid of branched chain amino acids and mega dose thiamine therapy.

Keyword: Maple syrup urine disease, branched chain amino acids, metabolic acidosis, body odor, stereotype movements.
Maple syrup urine disease (MSUD) is an autosomal recessively inherited error in the metabolism of branched chain amino acids (BCA) namely Valine, Leucine and Isoleucine.  

**Case Details:** Ten days old girl baby was admitted with lethargy and refusal of feeds of one day duration. There was no history of vomiting or seizures. She is the fourth born baby to second degree consanguineous parents. She transited well at birth and was on exclusive breast feeds. Her eldest brother died in neonatal period due to seizures. Her 7 year old, second brother is developmentally delayed with intractable seizures and is on multiple anticonvulsant drugs. Her 3 year old third brother is normal. On admission this baby had a sluggish activity with weak cry and shallow respiratory efforts. A sweet fruity odor was noted on her body. Enteral feeds were withheld and ventilator support was provided. She had recurrent episodes of hypoglycemia on first day of admission which necessitated the use of high glucose infusion rate upto 10 mg/kg/min. During the course of hospitalization, she was noted to make repeated stereotyped movement, mimicking a decerebrate posturing. The ventilator support could be withdrawn after 5 days of ventilation. Her blood cell counts, blood urea, creatinine and serum electrolyte levels were normal. Septic work up, including blood and CSF cultures were normal. Plasma ammonia was 195 µmol/L (Normal 21- 95 µmol/L). Blood lactate level was within normal limits. Urine 2,4-Dinitrophenylhydrazine (DNPH) test was negative. Urine had elevated levels of BCA and alpha keto acids. Tandem mass spectrometry (TMS) analysis showed elevated levels of Valine [798.9 nmol/ml (Reference range 86- 190 nmol/ml)], Isoleucine [375.6 nmol/ml (Reference range 26- 91 nmol/ml)] and Leucine [3931.8 nmol/ml (Reference range 48- 160 nmol/ml)]. These features were suggestive of Classic Maple Syrup Urine Disease (MSUD). She was started on special formula diet devoid of branched chain amino acids along with hind milk feeding. Thiamine 75 mg thrice daily was also added. After one month on such modified diet, her stereotyped movements disappeared and the abnormal body odor subsided. She is on regular follow up with special diet. Her elder brother with seizure disorder was evaluated for MSUD with TMS, which turned out to be normal.

**DISCUSSION:**
MSUD is due to deficiency of Branched chain alpha keto acid dehydrogenase (BCKD). This enzyme with its coenzyme Thiamine pyrophosphate(Vitamin B1) helps in the decarboxylation of alpha ketoacids of BCA to their respective branched chain acetyl CoA. BCKD has four different catalytic components ( E1,E1, E2 and E3). E3 catalytic component is common to two other dehydrogenases namely Pyruvate dehydrogenase and Alpha keto glutarate dehydrogenase. Deficiency of BCKD leads to the accumulation of BCA and their corresponding ketoacids in body. Accumulation of leucine is predominantly responsible for neurological symptoms. The elevated isoleucine level causes the peculiar maple syrup odor of urine. Based on the age of onset and severity of symptoms five different clinical types of MSUD have been identified: 1) Classic MSUD babies are normal at birth and present in the first week of life.
with lethargy, vomiting, poor feeding, other neurological signs like alternating hypotonia and hypertonia, dystonia, seizures, encephalopathy and cerebral edema. 2) Intermediate MSUD affected children have an insidious onset of milder symptoms after the neonatal period and present with developmental delay and seizures. 3) Intermittent MSUD is the second most common type of MSUD. These children have normal growth and development but develop symptoms during episodes of catabolic stress like infection or surgery. 4) Thiamine responsive MSUD is a very rare type and is due to mutation in E2 subunit of BCKD. 5) E3 deficient MSUD is a very rare type with associated elevated levels of lactate, pyruvate and alanine. MSUD babies have metabolic acidosis and hypoglycemia. DNPH test is positive in urine sample. However this test is less sensitive in neonatal period. Urine contains high levels of BCA and their respective ketoacids. Plasma amino acidogram shows marked elevation of BCA; elevated levels of alloisoleucine, a stereoisomer of isoleucine which is not normally found in body fluids and depressed levels of alanine. Newborn screening for MSUD is possible with TMS. Enzyme activity can be measured in cultured fibroblasts or lymphocytes. Prenatal diagnosis can be performed by measuring the enzyme activity in cultured amniocytes or chorionic villous cells, mutation analysis or by measuring BCA level in amniotic fluid. Treatment of acute state is aimed at hydration and quick removal of BCA and their ketoacids from the tissues and body fluids by BCA free diet. Peritoneal dialysis or hemodialysis is the most effective mode of therapy in critically ill infants. The dietary therapy is lifelong and aims to normalize BCA levels in body fluids without impairing the growth and intellectual development. Synthetic formulas devoid of BCA are available. Small amounts of BCA are added to diet, as these BCA are also essential amino acids. A trial of thiamine therapy for at least 3 weeks is recommended, before a favorable response is seen in thiamine responsive MSUD. With timely detection of mild or moderate illnesses, many individuals can be managed safely at home by experienced providers using dietary leucine restriction, high-calorie BCA-free "sick-day" formulas, and frequent outpatient monitoring. Liver transplantation is performed in small number of children with good results. The long term prognosis of affected children remains guarded. Death may occur during any stressful event like surgery or infection. Patients with intermittent MSUD have died during these episodes when not appropriately treated. Transient periods of MSUD encephalopathy appear fully reversible, provided no global or focal ischemic brain damage occurs. In contrast, prolonged amino acid imbalances, particularly if they occur during the early years of brain development, lead to structural and functional neurologic damage. Attention deficits, impulsivity, and hyperactivity are common in school-age children and mental illness is prevalent in adolescents and adults. About 37% of individuals above 12 years of age will need psychotropic medications for generalized anxiety, panic disorders or depression. Individuals with classic MSUD can reach adulthood with normal intelligence. However, mild to moderate intellectual disability is common in older persons. The chronic cognitive outcome is more directly related to indices of long-term amino acid homeostasis and cerebral essential amino acid sufficiency, rather than age at diagnosis, residual BCKD enzyme activity, or the number and severity of metabolic crises.
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