CASE REPORT

Bali Medical Journal (*Bali Med J*) 2018, Volume 7, Number 1: 240-243
P-ISSN.2089-1180, E-ISSN.2302-2914

Published by DiscoverSys

Maple syrup urine disease: The first case in Bali

Putu Andina Pramitasari,[1] I Gusti Lanang Sidiartha,[2*] Irene Widodo[3]

ABSTRACT

Background: Maple syrup urine disease (MSUD) is a rare genetic disease of metabolic disorder inherited as an autosomal recessive trait. The disease is caused by branched-chain alpha-keto acid dehydrogenase (BCKD) deficiency. It results in the accumulation of branched-chain amino acids (BCAA) which are toxic to the nervous system.

Case Presentation: A one-week-old infant was brought to Siloam Hospital because she suddenly became lethargic, had a poor feeding, and an intermittent muscle spasm. She was the fourth child in her family. At her admission, she was diagnosed with neonatal sepsis. On advanced clinical and laboratory examination, we found ketoacidosis, hypoglycemia, and the typical odor of maple syrup in the urine. Plasma amino acids analysis showed a marked elevation of BCAA (leucine, isoleucine, and valine), confirming the diagnosis of MSUD. The patient was treated with intravenous glucose infusions and dietary support, including formulas free of BCAA. She was monitored for blood sugar and urine ketones.

Conclusion: Metabolic disease should be considered in an infant who suddenly suffered a critical illness several days following a normal delivery.

Keywords: maple syrup urine disease, MSUD, BCAA

Cite This Article: Pramitasari, P.A., Sidiartha, I.G.L., Widodo, I. 2018. Maple syrup urine disease: The first case in Bali. *Bali Medical Journal* 7(1): 240-243. DOI:10.15562/bmj.v7i1.1136

[1]Pediatric Resident,
[2]Pediatrician and Nutrition Consultant,
Department of Child Health, School of Medicine, Udayana University/Sanglah General Hospital, Denpasar, Bali, Indonesia;
[3]Pediatrician, Siloam Hospital, Denpasar, Bali, Indonesia

[*]Correspondence to:
I Gusti Lanang Sidiartha, Pediatrician and Nutrition Consultant, Department of Child Health, School of Medicine, Udayana University/ Sanglah General Hospital, Denpasar, Bali, Indonesia
lanangsidiartha@yahoo.com

Received: 2017-08-24
Accepted: 2017-12-6
Published: 2017-12-12

INTRODUCTION

Maple syrup urine disease (MSUD) is an inborn error of metabolism.[1] It is biochemically characterized by elevated concentration of the branched-chain amino acids (BCAAs): leucine, isoleucine, valine.[1] The disorder is caused by a severe deficiency in the activity of the branched-chain α-keto acid dehydrogenase complex (BCKDH).[2] MSUD is an autosomal recessive disorder. The worldwide incidence of MSUD is approximately 1:185,000.[3] In the United States, MSUD occurs in about 1 case per 180,000 newborns. As an autosomal recessive disorder, MSUD is more prevalent in populations with a high frequency of consanguinity. MSUD has been reported to occur in all ethnic groups, although the incidence and prevalence may widely vary. No sex predilection is noted.[1]

MSUD is classified into four types: classic, intermediate, intermittent, and thiamine-responsive. Classic MSUD is the most severe one. Twelve hours after birth, an untreated neonate with classic MSUD will produce cerumen with maple syrup odor.[4,5,6] By 12-24 hours, there will be elevated plasma concentrations of leucine, isoleucine, and valine and allo-isoleucine, as well as a generalized disturbance of amino acid plasma concentration ratios.[4,5,6] In the two to three days of the infant's life, the infant will show ketonuria, irritability, and poor feeding.[4,5,6] By the age of four to five days, deepening encephalopathy happens, manifesting as lethargy, intermittent apnea, opisthotonus, and stereotyped movements such as "fencing" and "bicycling" can be observed.[4,5,6] By age, seven to ten days, coma and central respiratory failure may follow.[4,5,6] Individuals with intermediate MSUD have a partial BCKDH enzyme deficiency that only manifests intermittently or responds to dietary thiamine therapy.[5,6] These people may experience severe metabolic intoxication and encephalopathy during sufficient catabolic stress.[4,7]

MSUD is diagnosed by the presence of the clinical features, elevated BCAAs and allo-isoleucine in plasma, and branched-chain hydroxyl-acids and branched-chain α-keto acids (BCKAs) in urine.[2,4] L-leucine, L-isoleucine and L-valine in neonatal blood are important markers for MSUD. A marked increase in serum and urine concentrations of BCAAs and BCKAs are the biochemical hallmarks of the disorder.[2] Newborn screening (NBS) programs that employ tandem mass spectrometry detects MSUD by measuring the whole blood combined leucine-isoleucine concentration and its ratio to other amino acids such as alanine and phenylalanine.[2]

Without early and effective treatment children will develop severe and permanent brain damage including spasticity or they even die within the first months of life. Treatment for MSUD must start immediately. The two most important aspects of the treatment of MSUD are long-term management and the treatment of episodes of acute metabolic

decompensation.[8,9] Nutritional therapy plays an essential role in restoring and maintaining metabolic homeostasis in MSUD.[10] Dietary restriction of BCAA is necessary to achieve and maintain plasma BCAA concentrations as close to normal as possible while preventing and correcting BCAA deficiencies.[9,10] Metabolic decompensation episodes need to be addressed aggressively by initiating intravenous glucose infusions as rapidly as possible. Also, to promote anabolism, insulin infusions may be added. BCAA intake had to be stopped but resumed as soon as plasma BCAA becomes normal.[11] An additional dietary support should be done whenever possible by including lipids and or formulas free of BCAA. In rare circumstances, hemodialysis or peritoneal dialysis may be necessary to remove BCAA and BCKA.[4,10]

The goal of the dietary therapy is a normal plasma BCAAs (particularly of leucine) by restricting intake of BCAAs without impairing growth and intellectual development.[4,12] The long-term metabolic control of patients with the classic form of MSUD has a significant impact on the patient's cognitive outcome. Irrespective of neonatal encephalopathy, the normal cognitive outcome is achievable if long-term plasma leucine levels are close to normal. However, in patients without neonatal encephalopathy and thus with optimal starting-point conditions, the intellectual outcome seems to be heavily influenced by long-term plasma leucine levels.[6] The patient must follow the dietary therapy guideline throughout the patient's life.[8] Luckily, several commercial formulas and foods without or with reduced concentration of BCAAs are available.[4,8,13]

CASE REPORT

A one-week-old female infant was brought to Siloam Hospital in November 2016. Her mother said the baby suddenly became lethargic, had a poor feeding, and had an intermittent muscle spasm.

The baby was the fourth child in the family. The first child is alive and healthy. The second and the third child died when they were around three weeks old following the same symptoms concluded as a severe infection of an unknown origin.

During the mother's last pregnancy, she did a regular checkup to an obstetrician and not any irregularities found. The mother denied having symptoms or sickness in her pregnancy. She had never consumed any medication during the pregnancy other than the prescribed pregnancy supplements.

The infant was delivered by a Caesarean section, and she was spontaneously crying. The birth weight was 3046 gram.

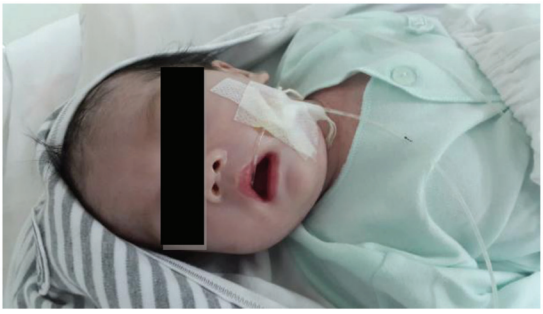

Figure 1 The one-week-old infant with MSUD

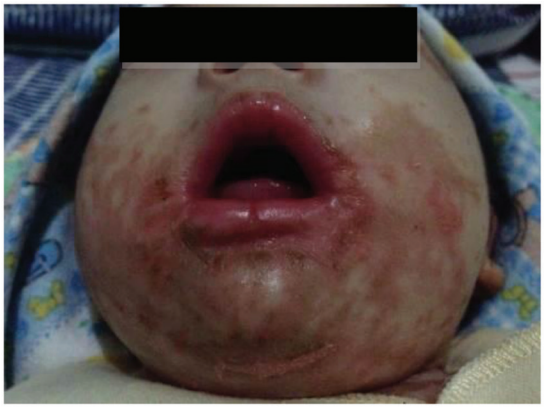

Figure 2 The skin lesions in MSUD

At admission, the infant was diagnosed with neonatal sepsis. However, the patient did not respond well during her stay, even after the intravenous antibiotic was administered. The laboratory examination showed ketoacidosis, hypoglycemia (blood sugar 50 g/dL), the urine odor was like the smell of maple syrup. Urinalysis showed a normal pH, proteinuria (+2), and ketonuria (+4). Plasma amino acids analysis was done to confirm the diagnosis. It showed a marked elevation of BCAA concentration (leucine, isoleucine, and valine) confirming MSUD. The leucine concentration was 1219.92 (29.0-266.0).

On 27 November 2015, the patient was referred to Sanglah General Hospital and the reexamination for the septic marker, urine, blood sugar and blood culture. Urine result pH 7 with ketonuria (+4) and blood sugar 55, from septic marker leukocyte, was 12.8 with neutrophil 62.3%, CRP 46.85 and I/T ratio 0.03 better than before, so antibiotics resumed. The patient was treated in the Neonatal Intensive Care Unit (NICU) in the incubator with nasal O^2 1 L per minute, antibiotic Cefoperazone sulbactam, Amikacin, Apialis, Zinc, intravenous glucose infusions IVFD D12,5% and NaCl 3% 13 ml, KCl 35 ml, calcium gluconate 3.5 ml and dietary support including formulas free of BCAA. Enteral nutrition gradually increased with monitoring for blood sugar and ketones urine.

On 22 December 2015, the patient was lethargic, re-examination for the septic marker we found enhancement leukocyte 42.1 with neutrophil 77.5%, CRP 132, and I/T ratio 1.16. We changed the antibiotic to Meropenem, and re-examination the blood sugar and urine. The blood sugar was 35 dan ketonuria (+3) so that the patient had to fast and received parenteral nutrition following a bolus of glucose.

On 31 December 2015, the patient showed improved clinical and septic marker, so antibiotics were discontinued. Enteral feeding with formula free BCAA increase gradually with monitoring ketonuria and blood sugar. During treatment keep monitoring the random blood glucose and urine ketones to evaluate nutrition, maintain to avoid ketosis conditions. Evaluation of BCAA showed a decreased leucine plasma concentration 785.33 (29.0-266.0).

On 26 January 2016, the patient was allowed to go home. In 2017 we contacted the hospital but had found that the patient had died.

DISCUSSION

Our patient came in a lethargic state. The mother concerned that her baby had a poor feeding and an intermittent muscle spasm. On advanced clinical and laboratory examinations, we found ketoacidosis, hypoglycemia, and noticed the urine had an odor resembling maple syrup. The clinical findings and the laboratory investigations directed us toward MSUD.

Following the standard treatment recommendation, we treated our patient with intravenous glucose infusion and dietary support. We included formulas free of BCAA.[8,9,10] Although the pathophysiology of MSUD can be addressed through rational formula design, this does not replace the need for careful clinical monitoring, frequent measurement of the complete amino acid profile, and ongoing dietary adjustments that match nutritional intake to the metabolic demands of growth and illness.[14] During the treatment, we evaluated the amino acid plasma concentration twice and carried out strict monitoring of the blood sugar and urine ketone concentration to evaluate and prevent ketosis affecting the condition of the patient.

Learning from our case, we found that it is challenging to diagnose MSUD early for two reasons. First, it is difficult for pediatricians to distinguish MSUD from common fatal diseases in the neonatal period. Because, a patient with MSUD does not show any specific clinical manifestations except producing a maple syrup odor, nor specific routine laboratory findings. Second, it took several days to obtain the results of diagnostic examinations. Because, most pediatricians cannot perform diagnostic examinations in their own laboratories.[1,4]

Our patient was diagnosed with MSUD at the age of one week. The classic MSUD clinical onset occurs within the first weeks after birth. The symptoms and signs comprise of a maple syrup odor, acute metabolic decompensation with feeding problems and drowsiness, followed by progressive coma with involuntary movements, seizures, and respiratory failure. The diagnosis is usually established by measuring plasma BCAA concentration including allo-isoleucine, which is pathognomonic for the disorder, and their corresponding BCKAs in urine.[1,4,15]

SUMMARY

We report a one-week-old female infant who came in a lethargic state, accompanied by feeding problems and intermittent muscle spasm. The initial diagnose at admission was neonatal sepsis. After advanced clinical and laboratory examination was done, we found ketoacidosis, hypoglycemia, and maple syrup odor in the urine. We did a plasma amino acid analysis. It showed a marked elevation of BCAA (leucine, isoleucine, and valine) affirming MSUD. The patient was treated with intravenous glucose infusions and dietary support, including formulas free of BCAA with closed monitoring for blood sugar and ketones urine during her hospitalization.

REFERENCE

1. Chuang DT, Shih VE. Maple syrup urine disease. Scriver CR, Beaudet AL, Valle DL, Sly WS, eds. *The Metabolic and Molecular Bases of Inherited Disease*. 8th ed. New York, NY: McGraw-Hill Co; 2000
2. Deng C, Deng Y. Diagnosis of maple syrup urine disease by determination of L-valine, L-isoleucine, L-leucine, and L-phenylalanine in neonatal blood spots by gas chromatography-mass spectrometry. *J. Chromatogr. B,* 2003; 792 : 261-268
3. Frazier DM, Allgeier C, Homer C, Marriage BJ, Ogata B, Rohr F, Splett PL, Stembridge A, Singh RH. Nutrition management guideline for maple syrup urine disease: an evidence- and consensus-based approach. *Mol Genet Metab* 2014;112:210-7.
4. Strauss KA, Puffenberger ED, Morton D. Maple syrup urine disease. In: Pagon R, Adam M, Bird T, et al., editors. GeneReviews. Seattle, WA: University of Washington. 2006; p. 1993-2013.
5. Morton DH, Strauss KA, Robinson DL, Puffenberger EG, Kelley RI. Diagnosis and treatment of maple syrup disease: a study of 36 patients. *Pediatrics* 2002;109:999e1008.
6. Hoffmann B, Helbling C, Schadewaldt P, Wendel U. Impact of longitudinal plasma leucine levels on the intellectual outcome in patients with classic MSUD. *Pediatr Res* 2006;59: 17-20.
7. Knaap, Marjo S, Valk, Jaap. Maple Syrup Urine Disease. *Magnetic Resonance of Myelination and Myelin Disorders*. 2005: 311-320

8. Harris RA, Joshi M, Jeoung NH, Obayashi M. Overview of the molecular and biochemical basis of branched-chain amino acid catabolism. *J Nutr*. 2005; 135(6 Suppl):1527S-30S.
9. Morton DH, Strauss KA, Robinson DL, et al. Diagnosis and treatment of maple syrup disease: a study of 36 patients. *Pediatrics* 2002; 109(6):999-1008.
10. Chuang DT, Shih VE. Maple syrup urine disease (branched-chain ketoaciduria). In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular basis of inherited disease. 8th ed. New York: McGraw-Hill; 2001; 1971-2006.
11. Genetic Metabolic Dietetians International, MSUD Nutrition Management Guidelines, https://southeastgenetics.org/ngp/guidelines.php/59/MSUD%20 Nutrition%20 Guidelines/Version%201.46 2014 (Accessed 20 May 2016).
12. Couce ML, Ramos F, Bueno, Dı´az J, Meavilla S, Fernandez MA. Evolution of maple syrup urine disease in patients diagnosed by newborn screening versus late diagnosis**.** *European Journal of Paediatric Neurology*. 2015:652-9
13. Simon E, Schwarz M, Wendel U. Social outcome in adults with maple syrup urine disease (MSUD). *J Inherit Metab Dis* 2007; 30: 264.
14. Strauss KA, Wardley B, Robinson D, Hendrickson C, Rider NL, Puffenberger EG, Shellmer D, Moser AB, Morton DH. Classical maple syrup urine disease and brain development: principles of management and formula design. *Mol Genet Metab* 2010;99:333e45.
15. Zinnanti WJ, Lazovic J, Griffin K, Skvorak KJ, Paul HS, Homanics GE, Bewley MC, Cheng KC, Lanoue KF, Flanagan JM. Dual mechanism of brain injury and novel treatment strategy in maple syrup urine disease. *Brain* 2009;132(Pt 4):903-18.