



Case Report

Pregnancy in an adolescent with maple syrup urine disease: Case report

Michelle E. Abadingo^{a,b,c,*}, Mary Ann R. Abacan^{a,b}, Jeanne Ruth U. Basas^b,
Carmencita D. Padilla^{a,b,c}

^a Division of Clinical and Metabolic Genetics, Department of Pediatrics, University of the Philippines – Philippine General Hospital, Manila, Philippines

^b Institute of Human Genetics, National Institutes of Health, University of the Philippines, Manila, Philippines

^c Newborn Screening Reference Center, National Institutes of Health, University of the Philippines, Manila, Philippines

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ABSTRACT

Maple syrup urine disease (MSUD, MIM #248600) is an autosomal recessive metabolic disorder that results in elevation of the branched-chain amino acids (BCAA) leucine, isoleucine, and valine. Elevation of BCAA and certain alpha keto-acids is associated with a catabolic state and may result in neurological and developmental delays, feeding problems, and a urine and cerumen odor of maple syrup. Pregnancy is a period of multiple adaptations necessary to support fetal growth and development. Both the third trimester of pregnancy and the postpartum period present the possibility for catabolic states. We describe our treatment of an adolescent patient with intermittent MSUD and her resulting positive pregnancy outcome.

1. Introduction

Maple syrup urine disease (MSUD, MIM #248600) is an autosomal recessive disorder that results in branched-chain α -ketoacid dehydrogenase (BCKAD) enzyme deficiency. This enzyme complex is the second step in the catabolic pathway of the branched-chain amino acids (BCAA) leucine, isoleucine, and valine. BCKAD is made up of several components: α -keto decarboxylase (E1) consisting of α and β subunits, dihydrolipoyl transacylase (E2), and a dihydrolipoyl dehydrogenase (E3). The following genes encode for the subunit: *BCKDHA* for E1 α , *BCKDHB* for E1 β , *DBT* for E2, and *DLD* for E3 (Fig. 1). Signs and symptoms of MSUD from increased concentrations of endogenous BCAA and alpha-ketoacids may include a maple syrup odor in urine and cerumen, encephalopathy, feeding problems, and neurological and developmental delay [1–3].

There are 5 distinct phenotypes of MSUD: classic, intermediate, intermittent, thiamine-responsive, and E3-deficient. While the clinical presentation of MSUD depends on residual BCKAD activity, the phenotypic classification relies on leucine tolerance and metabolic response to illness. It should be emphasized that during catabolic states, clinical and biochemical features of the classic form may arise in patients, and should be controlled similarly to individuals with the severe form [1]. Axler and Holmquist in 2014 [4] presented a case of intermittent MSUD that followed a clinically atypical course after a bout with common infection.

Newborn screening (NBS) was introduced in the Philippines in 1996 and was integrated into the public health system in 2004 through Republic Act No. 9288 or the Newborn Screening Act of 2004 [5]. MSUD was included in the newborn screening (NBS) panel since 2012 [6]. As of December 2019 there are 148 confirmed cases of MSUD by NBS in the Philippines resulting in a prevalence of 1:65,953 [7]. In the metabolic registry of the Clinical Genetics Unit, Institute of Human Genetics, there are 263 cases of MSUD from 1992 to June 2020 (Personal communication). Early detection of the disease aids in its timely intervention ideally allowing treatment to begin before the patient becomes symptomatic. However, in the study of Puckett and colleagues [8], it was noted that patients with mild, variant forms of MSUD may escape detection by NBS. For patients who are initially asymptomatic but present symptoms in stress situations, genetic testing is crucial in determining the gene-causing mutation of the deficient subunit [1].

Nutrition management is one of the primary goals in the medical treatment of MSUD. This is done by decreasing the BCAAs in the diet and providing adequate calories and macronutrients to prevent a catabolic state. Medical formula devoid of BCAA is given to provide the majority of the protein requirement and additional energy and micronutrients [9]. Natural protein, or food sources with BCAA, and caloric intake are titrated according to the patient's biochemical laboratory values and growth throughout infancy, childhood, and adulthood [10].

Pregnancy is a period of multiple adaptations that are necessary to ensure a continuous supply of essential metabolites to support fetal

* Corresponding author.

E-mail address: meabadingo@up.edu.ph (M.E. Abadingo).

growth and development. The study of Zeng et al. [11] shows that the 3rd trimester of pregnancy is associated with catabolic adaptations to the increased requirements for protein and energy needed for growth of maternal and fetal tissue. The recommended intake for pregnant adolescents is generally increased by an amount proportional to the incomplete maternal growth [12]. Increased protein intake is necessary to support the proliferation of maternal tissues and growth of the fetus while keeping the plasma BCAA within the treatment range to maintain metabolic homeostasis. In addition to preventing catabolism, increased energy intake is also necessary to support the increased needs associated with pregnancy. Catabolism should be minimized or prevented in all stages of pregnancy and the immediate postpartum period [10].

In this case study, we present the successful pregnancy results of a 17-year-old pregnant teenager with intermittent MSUD. This is the first documented case of pregnancy in a patient with MSUD in the Philippines.

2. Clinical case

The patient is a 17-year-old female diagnosed with intermittent MSUD. She was admitted by a pediatric neurologist for neonatal seizures. She was the youngest in a sibship of three born to a healthy, non-consanguineous couple of Filipino descent. She also presented with maple syrup odor in the urine. A referral was made to a clinical geneticist for further evaluation. A urine sample was sent to the Department of Biochemistry, College of Medicine, University of the Philippines Manila for thin-layer chromatography (TLC). Dietary management for MSUD and anti-convulsant therapy were initiated while the results were pending. Management included increasing the total caloric intake, placing the patient on protein rest for 24 h, and gradually increasing the source of natural protein in the diet. She was also started on a BCAA-free medical formula. A dried urine filter card was also sent to the New South Wales (NSW) Biochemistry Laboratory of the Westmead Hospital, Sydney, Australia for TLC. The presence of leucine, isoleucine, and valine on both samples confirmed the diagnosis of MSUD.

The patient was on regular follow-up and maintained on a protein-restricted diet since her diagnosis and has had no decompensation and seizure episodes. Leucine levels have ranged from 140 to 250 $\mu\text{mol/L}$

and she was last seen in the metabolic clinic at 13 years old. Since that time, she has been off of her medical formula but has continued to limit her protein intake.

She again consulted with the metabolic clinic on her 31st week of gestation. Her last prenatal sonography was performed at 27 2/7 weeks of gestation and showed a fetal body weight (FBW) of 1151 g. A 24-h food recall showed that the patient's protein intake was approximately 30 g/day and total caloric intake was 1600 kcal/day. She was advised to increase her total caloric intake. The pregnancy was classified as high-risk due to the patient's age and medical condition, and a referral was made to the perinatology service for co-management. She was also referred to the adolescent medicine service. Admission plans for both the patient and the baby were made.

Aside from an episode of urinary tract infection (UTI) at the 35th week AOG, the course of the pregnancy was otherwise unremarkable. The UTI was treated with a 7-day course of oral antibiotics. A congenital anomaly scan (CAS) on the baby showed unremarkable results. The patient was admitted on her 37th week of pregnancy for regular uterine contractions. She was received at the Obstetrics Admitting Section 5–6 cm dilated and a leucine level was obtained upon admission. As part of the admission plan, 2 intravenous (IV) access ports were established. She was started on D10LR at maintenance rate and Intralipid 20% at 2 g/kg, which provided an additional caloric intake of 1137.6 kcal.

An emergency cesarean section was performed on the patient's 4th hour of admission as a result of fetal bradycardia on intrapartum monitoring. She delivered a live baby boy, APGAR 9, 9, with a weight of 3 kg (P 50th), length of 49 cm (P 90th), and head circumference of 33.5 cm (P 90th), all appropriate for gestational age. Skin-to-skin contact was initiated and early latching occurred.

The newborn was roomed-in with the mother. The baseline leucine of the mother at admission was 144.60 $\mu\text{mol/L}$. Intralipid was consumed and IV fluid was maintained while the mother was still on a soft diet. The IV was discontinued when the mother was feeding normally. Urine ketone monitoring for the mother was negative during the immediate postpartum period.

Expanded newborn screening (ENBS) on the newborn occurred at the 24th hour of life. The initial ENBS leucine result was 69.15 $\mu\text{mol/L}$ (normal range < 350 $\mu\text{mol/L}$). Natural protein intake was initially

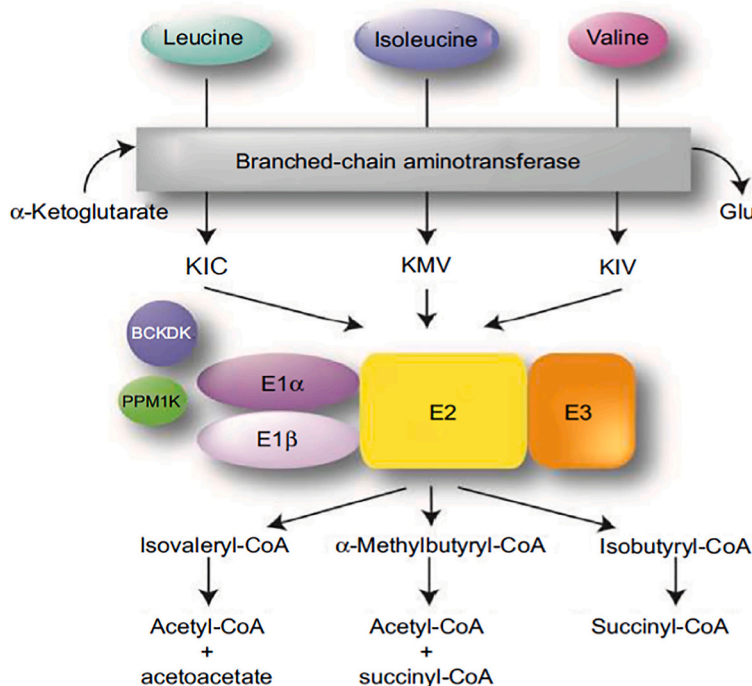


Fig. 1. Overview of the BCAA catabolic pathway. BCAA leucine, isoleucine, and valine undergo transamination that is catalyzed by branched-chain aminotransferase (BCAT). This reaction requires α -Ketoglutarate, leading to the production of α -ketoacids α -ketoisocaproic acid (KIC), α -keto- β -methylvaleric acid (KMV), and α -ketoisovaleric acid (KIV). These intermediates undergo oxidative decarboxylation, catalyzed by the branched-chain α -ketoacid dehydrogenase (BCKAD) complex.

Figure reprinted from Blackburn PR, Gass JM, Pinto e Vairo F, Farnham KM, Atwal HK, Macklin S et al. Maple syrup urine disease: mechanisms and management. *Appl Clin Genet.* 2017; 10: 57–66. This figure has been reproduced with permission from Dove Medical Press.

limited to 1 g/kg/day. His leucine level was again obtained on the 48th hour of life using a dried blood spot (DBS) and was 99.51 $\mu\text{mol/L}$ (normal range < 300 $\mu\text{mol/L}$). Direct breastfeeding was recommended.

The mother and her newborn were discharged unremarkable after the 7th hospital day. The leucine level of the mother on diet was 210.97 $\mu\text{mol/L}$ (normal range < 300 $\mu\text{mol/L}$). Blood samples were collected from the mother, her 2 siblings, and her child for genetic analysis. Samples were sent to Invitae (San Francisco, Ca) for the MSUD panel test. The panel test evaluated 5 genes that coded for the subunits of the BCKAD. Genomic DNA obtained from the submitted samples was enriched for targeted regions using a hybridization-based protocol and sequenced using Illumina technology.

The results of the genetic analyses showed that the mother is a compound heterozygote for the E2 gene; a pathogenic variant and a variant of uncertain significance (VUS) were identified. The pathogenic variant is a deletion of the genomic region encompassing exon 11. The 5' boundary is likely confined to intron 10. The 3' end of the mutation is unknown and extends through the termination codon beyond the assayed region for this gene and may encompass additional genes. The VUS is a p.Gly193Ser mutation at exon 6; the clinical impact of the mutation is unknown at this time. One sibling is a carrier of the VUS variant while her child is a carrier of the exon 11 deletion.

3. Discussion

The course of the pregnancy of an adolescent known to have intermittent MSUD is described in this report. Individuals with intermittent MSUD are asymptomatic and have normal growth and neurologic development even on an unrestricted diet [1]. However, clinical and biochemical features of MSUD may manifest in times of decompensation. The cornerstone of dietary management is providing adequate protein and calories to prevent catabolism. Catabolism should be prevented or minimized in all stages of pregnancy and the postpartum period [10].

Planning is essential in managing patients with MSUD. MSUD in pregnancy has been discussed in several case reports [13–19]. One case report discussed postpartum death secondary to cerebral edema, probably due to metabolic decompensation. The patient did not maintain her dietary treatment after hospital discharge [13]. Nutritional management was emphasized in all case reports. On the other hand, a recent study has discussed a successful pregnancy observing no dietary restrictions of 2 E α 1 subunit c. 1312 T > A homozygotes who underwent liver transplantation [20].

Our patient was seen in the Metabolic Clinic in her mid-third trimester of pregnancy. The estimated energy requirement (EER) for the third trimester is non-pregnant EER for adult women plus pregnancy energy deposition of 452 cal/day [12,17,21]. On the other hand, the recommended total protein is 120% DRI + 25 g/day [22]. The recommended dietary allowance (RDA) for a non-pregnant woman with MSUD is 55 g/day [21,22]. Thus, recommended total protein is 80 g/day (Table 1).

Given the patient's age, third trimester weight of 60 kg and height of 150 cm, her recommended energy intake is 2089.7 kcal/day. For pregnant MSUD patients, it is ideal that nutritional assessment and counseling are done monthly to per trimester. Diet is adjusted once to twice weekly depending on the BCAA levels [22]. Her leucine level was within the normal range. Expected fetal weight at 27 weeks age of gestation was appropriate for gestational age. While there are other confounding factors (i.e. environment, maternal age, and parity), maternal dietary intake can affect fetal birth weight [23]. The caloric and protein intake of the patient was sufficient to support the appropriate growth of the fetus. Stricter adherence to recommended nutritional values is needed for pregnant patients with classical MSUD.

As with previously reported cases [13,16,19], our patient was started on Intralipid 20% (2 g/kg) and D10LR during the peripartum period in order to place the patient in an anabolic state. Per the nutrition

Table 1

Recommended energy intake and dietary protein for a patient with maple syrup urine disease during pregnancy and lactation.

Intake	First trimester	Second trimester	Third trimester	Lactation
Energy, calories/day	Nonpregnant EER for sedentary women	+340 ^a	+452 ^a	+452 ^b
Total protein ^c , g/day	+ 0.5	+7.7	+25	+25 ^d

^a Formula for energy requirements for pregnancy is estimated energy requirement (EER) = nonpregnant EER for sedentary adult woman + pregnancy energy deposition. Energy is increased to 340 cal/day in the second trimester of pregnancy and 452 cal/day in the third trimester of pregnancy [9,10,17,21].

^b Energy recommendation for lactation is approximately the same as in the third trimester [22].

^c Recommended dietary allowance (RDA) for total protein. Total protein in the sum of natural protein and protein coming from BCAA-free medical food source. For patients with MSUD, total protein is 120%DRI + 0.5 g/day for the first trimester, 120%DRI + 7.7 g/day for the second trimester, and 120%DRI + 25 g/day for the third trimester. The protein RDA for a non-pregnant woman is 46 g/day. For a non-pregnant woman with MSUD, protein RDA is 55 g/day (120%DRI) [21,22].

^d Protein recommendation for lactation is approximately the same as in the third trimester [22].

management guideline for MSUD, attention was given to the prevention of catabolism during vulnerable periods of labor and delivery [9,10,22]. Both intravenous sources of energy were maintained while the patient could not tolerate oral feeding. Urine ketone monitoring was done to check for catabolism.

DBS for leucine is the most readily available method of monitoring in the Philippine setting. During pregnancy and postnatal period, it is recommended that aside from leucine level, valine and isoleucine levels are also monitored. The 2 amino acids should be maintained in the range of 200–400 $\mu\text{mol/L}$ throughout the pregnancy. Additional supplementation of valine and isoleucine may be needed to promote anabolism of leucine [10,22]. The results of the BCAA aid in the adjustment of the nutritional intake of the patient.

The results of the gene testing were consistent with the clinical presentation of the disease. The pathogenic variant is a deletion at exon 11. Gross deletions in the E2 gene were reviewed using the Human Gene Mutation Database (HGMD) [24]. The description of the patient's mutation is consistent with the results of the study of Chi and colleagues in 2003 [24,25]. This is similar to the previously reported Filipino MSUD founder mutation. In this study, the breakpoints within intron 10 and 3' non-coding region of the E2 locus were localized. Of the 15 patients, 7 had no amplified product of the terminal exon 11. This indicates a deletion of exon 11. Patients homozygous for the exon 11 deletion exhibited the classical MSUD clinical presentation [26]. The identified deletion affects more than 70% of the E2 alleles in Filipino MSUD patients [27].

The p.Gly193Ser mutation in exon 6 for MSUD has been identified in 2 cases which were also interpreted as VUS. The glycine residue is highly conserved; there is a small physiochemical difference between glycine and serine. Algorithms developed to predict missense changes on protein structure and population disagree on the possible impact of this missense change. This variant is not present in population databases [28]. More studies are needed on the clinical significance of this mutation. The clinical presentation of the patient is that of intermittent-type of MSUD because she is a compound heterozygote for 2 mutations.

4. Conclusion

This case highlights the significance of nutritional management of an adolescent patient with MSUD during pregnancy and the postpartum

period. Attention was preferentially given to the third trimester, intrapartum, and postpartum periods. Dietary adjustments were made to prevent a catabolic state. Incomplete maternal growth was also taken into consideration. The monitoring of biochemical parameters was essential to ensure proper dietary and energy management. Because of the various medical complexities that must be addressed, the utilization of a multi-disciplinary team can more effectively meet the medical needs of such a patient.

Declaration of Competing Interest

There are no financial conflicts of interest to disclose.

There are no competing interests to disclose.

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