Successful Pregnancy in a Woman with Maple Syrup Urine Disease: Case Report

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Abstract We present the positive outcome of a pregnancy in a woman with severe classic maple syrup urine disease (MSUD). Maintaining the maternal plasma levels of leucine between 200 and 300 $\mu\text{mol/L}$ allowed normal development of the foetus. Tolerance of protein and leucine increased continuously from the 16th gestational week until delivery. The patient was able to increase protein and leucine intake from 5 g to nearly 30 g and 300–3,000 mg/day, respectively. Weekly measurement of branched-chain amino acid (BCAA) concentrations and the assessment of dietary intake were used to adjust protein intake. After 41 weeks of pregnancy, she gave birth to a healthy baby girl and was able to breastfeed her daughter for 6 months during which time, the protein and leucine intake were lower than during pregnancy, but higher than with her usual pre-pregnancy diet. The development of the girl is normal at the age of 3 years.

Introduction

MSUD or branched-chain alpha-ketoaciduria is an autosomal recessive disorder of branched-chain amino acid (BCAA) catabolism first described in 1954 (Menkes et al. 1954). It is caused by a deficiency of branched-chain alpha-ketoacid dehydrogenase, which leads to an accumulation of the BCAAs leucine, isoleucine and valine and their toxic metabolites (Barbara 2010). Five distinct clinical phenotypes have been described in patients with MSUD, with 80% suffering from the severe classic type with 0–2% of normal enzyme activity (Chuang and Shin 2001). Untreated MSUD leads to severe mental and physical disabilities or death (Treacy et al. 1992). In 1964 administration of a diet restricted in BCAA was reported in seven patients with MSUD demonstrating that neurological manifestations could be prevented if nutritional management was instituted early (Snyderman et al. 1964), thereby establishing the basis for long-term nutritional management of patients with MSUD. In severe classical MSUD the nutritional therapy consists of strict protein restriction in combination with daily supplementation of a precursor-free amino acid mixture. Since then the outcome of patients with MSUD has gradually improved. Progress in newborn screening, early diagnosis and medical treatment, as well as an improved nutritional management, has resulted in normal growth and mental development in many of these patients (Hoffmann et al. 2006). As a result, an increasing number of women with MSUD reach child-bearing age. Since protein requirement increases during pregnancy, the management of such patients is a considerable challenge. Successful pregnancy outcomes in women with MSUD have been reported (Tchan et al. 2013; Grünewald et al. 1998; Van Calcar et al. 1992).

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Case Report

The patient is a 31-year-old Caucasian woman who suffers from severe MSUD, diagnosed within the first week of life. She received dietary treatment with strictly reduced intake of protein and branched-chain amino acids. She only had one significant metabolic decompensation at the age of 18 months. Physical and mental development remained normal. Also during adolescence – often a difficult period to keep patients motivated to follow the diet – leucine levels were most of the time within the target range. Higher BCAA levels were usually attributed to short episodes of illness such as influenza. The normal mental development and her decision to become a nurse were surely helpful in comprehending the particular features of MSUD and were supportive for dietary compliance. The patient's usual diet in adulthood includes a very low protein diet with about 5 g natural protein per day derived from fruits and vegetables. This corresponds approximately to 300–500 mg leucine. To keep the protein and leucine intake that low and to reach an adequate energy intake, she consumes medical dietary products such as low protein pasta, bread, cereals or sweets. To ensure an appropriate protein intake, she daily takes 70 g of a BCAA-free, micronutrient-enriched amino acid mixture (ILV-AM[®], SHS). She is aware of the importance of covering the energy requirements to avoid leucine increase from protein breakdown, i.e. she eats about five to six meals per day and she avoids catabolic fasting conditions. According to the regular laboratory results (leucine between 400 and 600 $\mu\text{mol/L}$), she consistently adhered well to her diet.

At the age of 29 she married an unrelated Caucasian man and became pregnant at the age of 30 years.

Pre-pregnancy anthropometric measures were height 153 cm, weight 58 kg and BMI 24.7 kg/m^2 . Her calculated resting energy requirement was 1,350 kcal, total energy expenditure 2,000 kcal (38 kcal/kg), which corresponds to the recommended daily energy intake for adults with MSUD (Barbara 2010). Energy need for pregnancy was derived from requirements for healthy women plus approximately 250 kcal/day for the entire pregnancy. She presented in the seventh gestational week to the metabolic team. Based on the experience of the University of Wisconsin, Madison, United States, the goal was to keep plasma leucine concentration during pregnancy between 200 and 300 $\mu\text{mol/L}$ which was slightly lower than usual. During the first 8 weeks, she followed her usual diet containing 300–500 mg leucine per day. First dietary counselling was set up after the first trimester of pregnancy. At this time the intake of leucine was around 1,000 mg/day. Plasma leucine concentrations were between 200 and 300 $\mu\text{mol/L}$, and she gained 1 kg in weight. She did not suffer from pregnancy sickness or vomiting.

Plasma leucine concentrations were measured weekly, and the patient maintained a food diary. Based on the plasma concentrations of BCAA, the intake of natural protein was increased. To keep plasma leucine concentrations in the target range, natural protein requirement continuously increased from the fourth month of gestation (Fig. 1). In a first step the low protein products were replaced by normal products. The daily intake of natural protein was increased to 15 g, corresponding to approximately 1,500 mg leucine, and the amino acid mixture was increased to 80 g. During the second half of pregnancy, a further increase to 30 g of natural protein was required to reach the target plasma BCAA values. This corresponded to approximately 3,000 mg leucine per day and was clearly much more than she had ever consumed before. In order to meet these increased protein needs, she had to consume more natural proteins. She disliked meat and fish, so that she ate more milk products and eggs. The maximal protein and leucine intake was in the eighth month of pregnancy. For a while she enjoyed this extraordinary situation; however, during the last month of pregnancy, she had no more appetite for those foods and she decreased the intake of natural protein to approximately 20 g/day. Despite this, the BCAA levels were maintained within the defined range (Fig. 2). During the whole pregnancy weight gain was about 10 kg.

After 41 weeks of gestation our patient gave birth to a healthy baby girl (weight 3,430 g, height 48 cm, head circumference 33.5 cm). To avoid catabolism during labour, she received intravenous glucose (220 g/24 h) from the moment the birth process started. The infusion was continued for the next 2 days. The maternal BCAA levels 5 h after birth were valine 205 $\mu\text{mol/L}$, isoleucine 63 $\mu\text{mol/L}$ and leucine 174 $\mu\text{mol/L}$. The baby's BCAA levels were checked on day two after birth and were below the normal range: isoleucine 14.9 $\mu\text{mol/L}$, leucine 43.8 $\mu\text{mol/L}$ and valine 85.2 $\mu\text{mol/L}$. For the first few days after delivery, the mother followed her pre-pregnancy diet with about 500 mg leucine per day. The postpartum goal for the BCAA levels of the mother was the same as those before pregnancy. Breastfeeding was instituted successfully at day two after birth. It was possible to discharge mother and baby after 5 days. The patient continued breastfeeding for the next 6 months. The BCAA levels were controlled approximately every third week. Three weeks after birth we found rather low levels of leucine (118 $\mu\text{mol/L}$) and valine (148 $\mu\text{mol/L}$). At this point the mother's intake of natural protein was 5–10 g/day. Based on the measured levels, the protein intake was increased to almost 15 g/day, and this was the average intake of natural protein per day during breastfeeding period. After stopping breastfeeding, she returned to her usual MSUD diet. The baby thrived very well, and at the age of 3 years she appeared to be normal in all aspects. The parents are planning a further pregnancy.

Fig. 1 Intake of total protein, aminoacid-mixture and normal protein (g). Intake of leucine (mg)

Fig. 2 Plasma leucine concentration (μmol/l) during pregnancy

Discussion

This is the sixth case of a successful pregnancy in a woman with classical MSUD documented in the literature (Tchan et al. 2013; Grünewald et al. 1998; Van Calcar et al. 1992). Remarkable in our case is the patient's excellent compliance with the diet. In order to maintain her compliance and motivation, we involved her in every possible process. This included the calculation of protein requirements and leucine intake as well as frequent regular follow-up visits with the metabolic team (physician, dietician and laboratory staff).

Successful outcomes of pregnancies in MSUD patients were presented by Tchan et al. (2013), Grünewald et al. (1998), and Van Calcar et al. (1992). Compared to the cases of Van Calcar and Tchan, our patient had a much lower pre-pregnancy protein intake (29, 15–35 and 30–50 g, respectively, versus 5 g natural protein in our patient). This was because of higher leucine tolerance or suboptimal compliance of the patient(s). While Van Calcar found a very high leucine tolerance of 8,600 mg/day at the end of the pregnancy suggesting a mild form of MSUD, Grünewald's patient's highest leucine tolerance (2,100 mg leucine per day) just before giving birth in the 36th week was closer to that to our patient. We found a progressive increase of leucine tolerance up to 3,000 mg of leucine per day and a maximal natural protein intake of approximately 30 g/day around week 30. As with Grünewald et al., we assume the increased tolerance of natural protein during pregnancy reflects enhanced protein synthesis in the fetomaternal compartment because of the capacity for branched-chain amino acid metabolism in the foetus that partially compensated the mother's metabolic deficit. In contrast to other cases, we found no increase in leucine level postpartum. Those high leucine levels were thought to be the result of protein breakdown due to postpartum uterine involution and perhaps also poor dietary compliance (Tchan). In order to avoid a postpartum rise of leucine, we therefore decided to attempt to avoid the catabolic state during labour and birth by giving an infusion of 10% glucose (3.3 g/kg/day). We also reduced leucine intake to pre-pregnancy values immediately postpartum until breastfeeding was successfully instituted. Since one hundred ml of mother's milk contains about 1.5 g protein and 300 mg leucine, we expected an increase of protein and leucine requirement during the breastfeeding period.

Our case and the described examples clearly demonstrate that careful and close monitoring of MSUD patients is very important during pregnancy and the experience gained is helpful to handle further cases. Although it is clear that it remains essential to treat every case individually, this needs to be based on the careful and detailed documentation of management and outcome of pregnancies in women with MSUD as reported here.

Finally a metabolic team with experience of patients with inherited metabolic diseases, with close collaboration of physicians, laboratory staff, dietician and the patient, is essential for successful outcome in pregnancy of MSUD and related disorders.

Compliance with Ethics Guidelines

Informed Consent: The patient was informed and agreed to the use of her anonymised data for the purpose of this publication.

Conflict of Interest

Stefanie Heiber, Henryk Zulewski, Marianne Zaugg, Caroline Kiss and Matthias Baumgartner declare that they have no conflict of interest.

Author Contributions

Stefanie Heiber – Dietician counselling, adapted dietary recommendations based on laboratory findings. Wrote the manuscript, guarantor

Henryk Zulewski – Followed the patient before, during and after pregnancy, discussed the manuscript

Marianne Zaugg – Laboratory investigation, interpretation of laboratory findings, discussed the manuscript

Caroline Kiss – Discussed the manuscript

Matthias Baumgartner – Followed the patient before, during and after pregnancy, discussed the manuscript

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