The Management of Pregnancy in Maple Syrup Urine Disease: Experience with Two Patients

Michel Tchan · M. Westbrook · G. Wilcox · R. Cutler ·
N. Smith · R. Penman · B.J.G. Strauss · B. Wilcken

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Abstract We describe the management and outcomes of pregnancy in two women affected with Maple syrup urine disease (MSUD). Both patients had classical disease diagnosed in the newborn period and were managed with low-protein diets and supplements, although compliance was moderately poor throughout life. Both pregnancies were complicated by poor compliance and one patient had a metabolic decompensation, which included seizures and profound encephalopathy, at the end of the first trimester. Peri-partum management required a coordinated team approach including a high-calorie and low-protein diet. Both patients had elevated leucine levels in the post-partum period – one due to mastitis and the other due to poor dietary and supplement compliance combined with uterine

involution. On later review, leucine had returned to pre-pregnancy levels. Both infants were unaffected and have made normal developmental progress in the subsequent 1 to 2 years.

Introduction

MSUD is an autosomal recessive disorder caused by mutations in one of three of the four genes encoding subunits of branched-chain keto-acid dehydrogenase (BCKAD) (Zhang et al. 1989a, b; Herring et al. 1991; Nobukuni et al. 1991) and presents classically in the newborn period with a maple syrup odour in cerumen and urine, irritability and poor feeding by day 3, progressive neurological signs, encephalopathy, coma and death if untreated (Strauss et al. 2009). Treatment is by institution of a very low-protein diet, branched-chain amino acid-free supplement, and provision of calorie support at times of decompensation. Successful treatment means that patients are surviving into adulthood. Nevertheless, there have been very few reports of pregnancy in MSUD.

We report the successful outcome of pregnancy in two women affected with MSUD. A significant episode of metabolic decompensation at the end of the first trimester for one patient did not appear to have any effect on the health of the infant when assessed at 4 and 20 months of age, thus suggesting that maternal MSUD does not have a detrimental effect on the developing fetus.

Patient 1

The patient was born following an uneventful pregnancy and was diagnosed with classical MSUD by urine metabolic screen after she presented with seizures at 10 days

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M. Tchan (✉) · M. Westbrook
Department of Genetic Medicine, Westmead Hospital, PO Box 533,
Westmead, NSW 2145, Australia
e-mail: michel.tchan@health.nsw.gov.au

M. Tchan · M. Westbrook
Discipline of Genetic Medicine, Sydney Medical School, University
of Sydney, Sydney, Australia

B. Wilcken
Western Sydney Genetics Program, The Children's Hospital at
Westmead, Sydney, Australia

B. Wilcken
Disciplines of Paediatrics and Child Health and Genetic Medicine,
Sydney Medical School, University of Sydney, Sydney, Australia

G. Wilcox · R. Penman · B.J.G. Strauss
Monash University Department of Medicine, Southern Clinical
School, Monash University, Clayton, VIC, Australia

R. Cutler · N. Smith
Clinical Nutrition & Metabolism Unit, Monash Medical Centre,
Clayton, VIC, Australia

Fig. 1 Leucine levels (■ – $\mu\text{mol/L}$, left axis) and natural protein intake (x – g, right axis) plotted against gestational age. The peak at week 15 corresponds to her leucine level upon return from overseas

of age. She was managed with a low-protein diet and branched-chain amino acid-free supplements (MSUD Maxamum and MSUD Express). She had a number of significant decompensations during the first few years of life and was left with some neurological impairment and very mild intellectual impairment. She adhered loosely to a low-protein diet supplemented with MSUD Express Coolers (Vitaflo Australia). Her usual intake of natural protein was 15–35 g daily with 60 g protein from MSUD Express Coolers. Her leucine levels were persistently 500–1000 μM ; unfortunately, improved compliance was difficult to achieve. Her past medical history included panic attacks, which were managed with fluvoxamine, and psoriasis. Up until her pregnancy, she worked full time at a department store.

She presented to our clinic at 10 weeks gestation. Plasma leucine levels were elevated (708 μM) and a low-protein diet (23 g natural protein equivalent and 60 g MSUD Coolers) was commenced, with the intention of regular monitoring of branched-chain amino acid levels via dried blood spot analysis.

Our patient planned to travel overseas to visit her non-consanguineous husband's family. She travelled with her dietary supplements and explicit letters of instruction for any episodes of illness. Unfortunately, she experienced an episode of fever and gastroenteritis after 1 week (14 weeks gestation). She could not maintain oral intake and progressively deteriorated, had a number of seizures and was said to have been unconscious for up to 24 h. She was treated with IV fluids and nasogastric administration of MSUD Express Coolers at a hospital in Pakistan. She recovered sufficiently to return to Australia, and when reviewed shortly after her arrival she was quite well with no

neurological sequelae. Her leucine level at that time was 586 μM . There were no further episodes of decompensation during the pregnancy.

Dietary management for the remainder of the pregnancy included a low-protein diet with increases in allowances over the duration of the pregnancy according to amino acid levels (Figs. 1, 2). MSUD Express Cooler intake was increased from 60 g to 75 g at 15 weeks gestation. Monitoring of protein intake was by patient estimates of intake provided by phone and email, as she lived remote from the clinic. Pregnancy weight gain was around 15 kg and there was not significant vomiting at any stage.

A management plan for the peri-partum period was instituted and distributed to involved members of the obstetric, medical, nursing and dietician staff (Table 1). She went into spontaneous labour at 40 weeks gestation and successfully gave birth by vaginal delivery to a baby boy following a 7-h labour. Natural protein intake was zero on day 1 post partum and increased by 5 g increments to her usual pre-pregnancy intake of approximately 20 g over 1 week. The post-partum period was uneventful and she was discharged on day 8. She subsequently presented to her local hospital on day 12 post partum and was diagnosed with mastitis on the basis of fever and a painful breast. Her leucine level peaked at 549 μM . This episode was treated with antibiotics, increased calorie intake and a reduction in natural protein intake with a quick resolution over 3 days.

The baby's Apgar scores were 9 and 9 at 1 and 5 min. The birth weight was 3336 g, head circumference 34 cm and length 51 cm. Initial testing demonstrated normal levels of branched-chain amino acids, but elevated alloisoleucine that subsequently decreased (at birth = 15 μM , at 24 h = 2 μM , and 48 h = 1 μM). His newborn screen did

Fig. 2 Leucine levels (■ – $\mu\text{mol/L}$, left axis) and natural protein intake (x – g, right axis) plotted against days post partum. An episode of mastitis was diagnosed on day 12

Table 1 Management plan for the peri-partum period of patient 1

During labour and for 24 h post partum

- EUC and blood glucose taken at every 6 h
- Amino acids taken daily

Early labour

- Insertion of adequate venous access by anaesthetic team
- Food as usual
- High-energy (no protein) supplements – Energivit 30 % aiming for 1 L per 24 h
- MSUD Express Cooler supplements ($5 \times 130 \text{ mL}$ per 24 h = 75 g protein)

Established labour or early labour and not tolerating oral intake

- IV 4 % dextrose in 1/5 normal saline (+/- additional K^+) at 100 mL/h
- Intralipid 20 % (3 g/kg/day)
- More intensive glucose + insulin therapy if required

First 24 h post partum if tolerating oral intake

- Protein-free food (0 g natural protein)
- High-energy (no protein) supplements – Energivit 30 % aiming for 1 L per 24 h
- MSUD Express Cooler supplements ($5 \times 130 \text{ mL}$ per 24 h = 75 g protein)

First 24 h post partum: if not tolerating oral intake, then TPN given over 24 h containing

- 1 L 10 % dextrose
- 500 mL 20 % Intralipid
- Standard electrolytes
- Leucine-isoleucine-valine-free amino acids (60 g/day)

Day 2 and thereafter post partum

- Gradual increase in dietary protein as directed by the metabolic team/dieticians
- High-energy (no protein) supplements – Energivit 30 % aiming for 1 L per 24 h
- MSUD Express Cooler supplements ($4 \times 130 \text{ mL}$ per 24 h)

not show evidence of MSUD. We interpreted the initially elevated alloisoleucine as being maternal in origin. On assessment at 4 months and then 20 months, he was thriving and showed appropriate development for his age.

Patient 2

The patient initially presented at 3 days of age becoming unwell with vomiting and increasing lethargy, progressing to seizures and loss of consciousness at 9 days of age, and was diagnosed with classical MSUD by urine metabolic screen on day 15. Her childhood course of disease was characterised by frequent recurrent metabolic decompensation, with over 70 hospitalisations by age 12 years. She had evidence of significantly delayed development. Formally, neuropsychological testing was consistent with moderate intellectual disability, presumed secondary to MSUD.

She adhered to an unmeasured low-protein diet supplemented with MSUD Express Coolers (VitaFlo Australia) and valine. By age 20 years, her usual intake of natural protein was estimated to be 30–50 g daily with 20–30 g protein from MSUD Express Coolers. Her compliance was suboptimal and leucine levels were typically 700–1300 μM . Her past medical history included panic attacks, exacerbated by poor metabolic control.

At 21 years of age, she presented to the paediatric metabolic clinic at 27 weeks gestation, based on ultrasound diagnosis of pregnancy 5 weeks earlier, and transferred to adult services. One week later, she presented with an acute febrile illness and threatened premature labour. Diagnosed with a urinary tract infection, she was also found to be mineral, vitamin and protein deficient. Subsequently, she failed to attend most scheduled antenatal and metabolic clinic visits. However, where amino acids were performed

Fig. 3 Leucine levels (■ – μmol/L, left axis) and natural protein intake (x – g, right axis) plotted against gestational age

Fig. 4 Leucine levels (■ – μmol/L, left axis) and natural protein intake (x – g, right axis) plotted against days post partum

during the second and third trimesters of pregnancy, none was elevated with respect to leucine (Figs. 3, 4). Pregnancy weight gain was around 14 kg and there was not significant vomiting at any stage.

She was admitted at 41 weeks gestation with suspected rupture of membranes but had failure to progress after 12 h which necessitated delivery by emergency lower segment caesarean section. Natural protein intake was zero on day 1 and increased to 9 g daily over 3 days. The patient self-discharged against medical advice on day 12 post partum despite elevated leucine levels, although she was not clinically encephalopathic at that time. There was considerable staff concern related to her social situation and capacity to care for the child in the setting of her intellectual disability. Implantable contraception was instituted prior to discharge.

The baby's Apgar scores were 9 and 9 at 1 and 5 min. The birth weight was 3405 g, head circumference 34 cm and length 50.5 cm. The newborn screen did not show evidence of MSUD. Apart from obesity and reflux in the setting of overfeeding, at 14 months of age the child has met expected developmental milestones.

Discussion

There are three pregnancies in women with classical MSUD documented in the literature, two of which ended without incident (Van Calcar et al. 1992; Grunewald et al. 1998) and the third of which reported maternal death at day 51 post partum (Yoshida and Tanaka 2003), although this death is more likely to have been due to trauma and

subsequent metabolic decompensation than a pregnancy-related decompensation. We describe here two additional cases demonstrating that pregnancy with a successful outcome can be achieved. Both our patients were classified as having “classical” MSUD, on the grounds that they presented with symptoms in the neonatal period. However in both, the protein tolerance before pregnancy was higher than that of most “classical” patients and suggests a more moderate MSUD phenotype.

We predicted two periods during which management would need careful monitoring and adjustment. Firstly, the increased tolerance of natural protein during the later stages of the pregnancy was predicted as the requirements of the fetus grow considerably during this time and maternal physiology changes to accommodate this. Other endocrine changes during pregnancy promote insulin resistance and an anabolic state (Di Cianni et al. 2003), also allowing increased protein tolerance. Careful monitoring was also required in the post-partum period. The patient described by Grunewald et al. had an increase in plasma leucine which peaked at day 9 post partum (Grunewald et al. 1998). This was thought to be as a result of a release of protein from the involuting uterus (Lee 2006), and thus we monitored our patients closely throughout the first 2 weeks post partum. The episode of decompensation in patient 1 precipitated by mastitis at day 12 post partum may have been exacerbated by the increased protein load of the involuting uterus. The poor metabolic control of patient 2 in the post-partum period was thought to be due to poor dietary and supplement compliance combined with uterine involution.

Both our patients had imperfect metabolic control throughout their pregnancies; however, fetal outcomes were good, despite maternal leucine levels that were grossly elevated at times. This contrasts favourably with the situation for maternal phenylketonuria and indicates that leucine is not a similarly potent teratogen. The apparently normal early development of these two children does not, however, preclude subtle long-term effects; therefore, children of such pregnancies should continue to be followed long term.

Documentation of management and outcome of pregnancies seem important, as there are as yet few reports in this or other inborn errors, with the exception of phenylketonuria. The true risk of an adverse effect on an infant, or an adverse post-partum event in the mother is not yet known for MSUD, and these two further cases help to define the situation.

Author Contributions

Michel Tchan – co-author, analysed data, clinician, guarantor

Mary Westbrook – revised article

Gisela Wilcox – co-author, analysed data, clinician

Rachel Cutler – revised article

Narelle Smith – revised article

Rebecca Penman – revised article

Boyd Strauss – clinician, revised article

Bridget Wilcken – clinician, co-author

Conflict of Interest

The authors declare they have no conflicts of interest.

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