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Rare disease

Multidisciplinary management of ornithine transcarbamylase (OTC) deficiency in pregnancy: essential to prevent hyperammonemic complications

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Summary

Ornithine transcarbamylase (OTC) deficiency is the most common inborn error in the metabolism of the urea cycle with an incidence of 1 in 14 000 live births. Pregnancy can trigger potentially fatal hyperammonemic crises. We report a successful pregnancy in a 29-year-old primiparous patient with a known diagnosis of OTC deficiency since infancy. Hyperammonemic complications were avoided due to careful multidisciplinary management which included a detailed antenatal, intrapartum and postnatal plan. Management principles include avoidance of triggers, a low-protein diet and medications which promote the removal of nitrogen by alternative pathways. Triggers include metabolic stress such as febrile illness, particularly gastroenteritis, fasting and any protein loading. In our case the patient, in addition to a restricted protein intake, was prescribed sodium benzoate 4 g four times a day, sodium phenylbutyrate 2 g four times a day and arginine 500 mg four times a day to aid excretion of ammonia and reduce flux through the urea cycle.

BACKGROUND

Ornithine transcarbamylase (OTC) deficiency is a disorder of the urea cycle with an estimated incidence of 1 in 14 000 live births.[1] Both improved medical care and newborn screening have led to an increasing number of patients with inherited metabolic diseases surviving into adulthood and therefore reaching a reproductive age.

Management principles include avoidance of triggers, a low-protein diet and medications which promote the removal of nitrogen by alternative pathways. Triggers include metabolic stress such as febrile illness, particularly gastroenteritis, fasting and any protein loading.

Pregnancy can be challenging in OTC deficiency as both the intrapartum and postpartum periods are catabolic states, which may trigger hyperammonemic episodes known to cause life-threatening encephalopathy.[2] Classically, decompensation occurs between days 3 and 14 postpartum but can occur up to 6–8 weeks later.[3] It is important that this is recognised and treated promptly to prevent cerebral oedema becoming established and irreversible which may result in a permanent neurological damage and even death. Information on the management of OTC deficiency in pregnancy is largely based on isolated case reports and small case series and further evidence is required to guide management.[2]

This is only the 21st case of an OTC deficiency and pregnancy, and there are less than 15 reported cases of pregnancy in symptomatic women with an OTC deficiency where the condition was known prior to pregnancy.[1–9] In our reported case, sodium phenylbutyrate and sodium benzoate were used throughout the pregnancy to aid excretion of ammonia despite extremely limited manufacturers' data on their use in pregnancy. Previous case reports indicate that they appear to be safe, but this case adds to the evidence supporting their lack of teratogenicity.

CASE PRESENTATION

A 29-year-old primiparous patient with a known diagnosis of OTC deficiency since infancy presented to our high-risk obstetric tertiary referral centre during the first trimester. The patient was under a long-term follow-up with a specialist metabolic unit and her condition was well-controlled on a restricted protein diet of 40 g of natural protein per day (0.67 g/kg), sodium benzoate 4 g four times a day, sodium phenylbutyrate 2 g four times a day and arginine 500 mg four times a day. The prescribed medications acted to aid excretion of ammonia and reduce flux through the urea cycle. She used an oral emergency regimen (reduced protein intake, 25% glucose polymer) during an intercurrent illness to prevent hyperammonemia approximately once per year. At her last hospital admission requiring an intravenous management for hyperammonaemia she was aged 15 years. Neurological physical examination was normal and she had a verbal IQ of 108 and a performance IQ of 67.

This was a planned pregnancy with the patient and her partner receiving an extensive pre-conceptual counselling. She had a body mass index of 22.4 kg/m^2 at 10 weeks gestation and suffered no other medical conditions or allergies. Essential amino acid, multivitamin and ω3 supplements had been started in the first trimester. A plan regarding her antenatal, intrapartum and postnatal management was put in place.

She had no problems with anorexia, nausea or metabolic decompensation in early pregnancy and chorionic villus sampling showed that she was carrying an unaffected male fetus.

The patient had an uncomplicated antenatal course and was reviewed regularly by a multidisciplinary team comprising of obstetricians, obstetric physicians, anaesthetists, midwives and a metabolic physician and dietician. Her plasma ammonia remained normal throughout the pregnancy. At 13 weeks gestation she was advised to increase her dose of arginine to 1 g four times a day due to borderline low-plasma levels and her protein allowance was increased to 60 g a day in the late third trimester.

Her 20-week anomaly ultrasound did not show any gross abnormality and a growth scan at 33+2 weeks gestation showed a head circumference (HC) and femur length (FL) on the third centile, with an estimated fetal weight below the 10th centile. Fetal growth assessments were thereafter performed twice weekly, showing a good interval growth with HC and FL maintaining measurements close to the third centile. As, in addition, the abdominal circumference (AC) always remained close to the 50th centile, the fetus was not thought small to be due to an intrauterine growth restriction caused by an over-restriction of protein.

At 40+4 weeks gestation, she underwent an induction of labour to provide a controlled environment should she develop any complications. Upon admission, intravenous 10% dextrose and oral glucose polymer were given to maintain her caloric intake above 2000 kcal/24 h. Regular antiemetics to prevent vomiting in addition to her regular medications were also given. A full blood count, random serum glucose and ammonia levels were all within the normal range both on admission and 12 h later. She required two prostaglandin gels, an artificial rupture of membranes (ARM) and a syntocinon infusion. Opiate analgesia and an epidural prior to ARM were used for pain relief.

The patient developed fever at fully dilated with two temperature readings above 38°C and a fetal tachycardia was noted. Broad-spectrum intravenous antibiotics were started and paracetamol given. As the cardiotocogram remained non-reassuring, the decision was made to expedite delivery and a rotational ventouse delivery was performed in the operating theatre. A healthy baby boy weighing 3050 g and with an Apgar score of 10, 10 and 10 was delivered in an occipito-posterior position. The patient sustained a 3b perineal tear which was sutured without complications and the estimated blood loss was 600 ml.

The patient made an uncomplicated immediate postnatal recovery, remaining afebrile with no growth on midstream urine and blood cultures. A 7 day course of oral co-amoxiclav and daltaparin for thromboprophylaxis was completed. The dextrose infusion was continued until she was eating and drinking in the postpartum period, when she was switched back to oral glucose polymer. Her low-protein diet was re-introduced slowly in a step-wise manner, with an agreed intake of only 25–30 g of protein per day for the first postpartum week. The oral glucose was stopped on day 2.

Daily ammonia levels were recorded. Her ammonia remained normal for the first 3 days postpartum. On day 4, it began to rise and continued to rise slowly from days 4 to 7. It peaked at 91 µmol/l on day 7 (normal value <35 µmol/l). Oral glucose polymer was re-introduced at day 4, along with an increase in sodium benzoate to 4 g four times a day. Importantly, she remained asymptomatic throughout her postpartum period and was discharged home on day 8.

On day 12, the sodium benzoate was decreased to her pre-pregnancy dose of 2 g four times a day. Natural protein intake was increased to pre-pregnancy levels (40 g) by 3 weeks postpartum.

OUTCOME AND FOLLOW-UP

In the week following the discharge she was assessed three times in the maternity assessment unit for clinical and biochemical markers of decompensation but remained clinically well with ammonia levels within the normal range (17–30 µmol/l). She continued to be assessed in the maternity assessment ward with twice weekly serum ammonia levels until 1 month postpartum. When reviewed at 6 weeks in the metabolic unit, both mother and baby were well. She had attempted to breastfeed but was not successful due to problems with the baby latching on.

DISCUSSION

Ornithine transcarbamylase (OTC) deficiency is the most common inborn error of metabolism of the urea cycle. This is the series of enzymatic reactions by which the body converts toxic ammonia, formed from the breakdown of protein, into urea which is then safely excreted. It is an X-linked dominant disorder, with an estimated incidence of 1 in 14 000 live births.[1] Therefore, men are usually more severely affected than women. Men often present with fatal hyperammonemia in the neonatal period whereas most women are either asymptomatic or have a later onset or less-severe presentation.[1 2]

Symptoms can be non-specific and include migraine-like headaches, recurrent vomiting, lethargy, hyperventilation, abnormal behaviour, disorientation or ataxia and anorexia especially to high-protein foods such as meat.[1 2] Episodes of acute metabolic decompensation can occur which may lead to life-threatening encephalopathy caused by high levels of ammonia.[7–9] An early intervention to treat the underlying cause and hyperammonemia is essential to prevent cerebral oedema becoming established and irreversible. Triggers include states of metabolic stress such as febrile illness, fasting or protein loading, but an obvious precipitant is not always found. Treatment of OTC deficiency includes avoidance of triggers, a low-protein diet and medications to aid the excretion of ammonia.[1]

Both an improved medical care and a newborn screening have led to an increasing number of individuals with inherited metabolic diseases surviving into adulthood and wishing to have children. There is little information about the management of OTC deficiency in pregnancy and is largely based on isolated case reports and small case series.[1–9] Further evidence is required to guide management and we would encourage the reporting of pregnancy management and outcome to add to the information available to aid counselling of these women.

Pregnancy, in particular the puerperium, can be a challenging time in the management of OTC deficiency and multidisciplinary management is essential.[1–6] A pre-pregnancy counselling to plan management, review treatment and ensure optimal nutritional status is strongly recommended.[3] A prenatal diagnosis should also be

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offered as the affected mother has a 50% chance of having an affected fetus.[1 2] Anorexia and nausea in the first trimester may precipitate a hyperammonemic crisis and care must be taken to avoid dehydration.[3] In addition, it is prudent to monitor for an intrauterine growth restriction in the fetus with serial growth scans due if the mother is on a restricted protein diet.[3] Usually, however, the antenatal course is uncomplicated. This is thought to be due to the increased nitrogen demands of the placenta, uterus and fetus reducing the chance of ammonia accumulation.[1] It is essential that any seizures are differentiated from eclampsia and therefore a regular blood pressure monitoring and urinalysis is important.[2]

There should be a clear management plan in place for delivery, as labour is associated with increased energy requirements in addition to vomiting and dehydration.[1 3] It is therefore imperative to ensure that labour is not prolonged, the patient remains well-hydrated with an adequate caloric intake and regular antiemetics are prescribed. An early epidural is also important as this reduces catabolism and the endocrine response to the surgical stress.[1] It is suggested that an elective delivery may be beneficial to plan the availability of specialist input.[2]

There is no proven cause as to why the puerperium is such a high-risk period. However, a logical hypothesis is that the combination of removal of the nitrogen-consuming fetal–placental unit together with the involution of the uterus (releasing excess nitrogen) causes an increase in the total nitrogen leading to hyperammonemia.[1] Therefore, it is important that serum ammonia levels are measured frequently in the postnatal period and the patient is aware to look out for any signs and symptoms of hyperammonemia. Metabolic decompensation typically occurs between days 3 and 10 but may occur up to 6–8 weeks later. Care must be taken that behavioural changes associated with high levels of ammonia are not attributed to postnatal depression or puerperal psychosis.[2] Breastfeeding also places extraenergy demands on the mother and therefore it is important to ensure an adequate calorie intake.[3]

To our knowledge, only 20 cases of OTC deficiency and pregnancy have been described in the literature till date and none from the UK.[1–9] Of these, 18 resulted in live births.[1–8] In 12 of these cases, the diagnosis of OTC deficiency was known prior to pregnancy. Of these, six had an uncomplicated antenatal, intrapartum and postnatal course, owing to clear management plans.[2 4 6] The most common complication was postnatal hyperammonemic crises.[1 3 5 7] Eight cases were only diagnosed postnatally due to hyperammonemia and five of these women died due to the resulting cerebral oedema.[5 7 9]

Learning points

- Ornithine transcarbamylase (OTC) deficiency is an X-linked dominant condition and is the most common inborn error of metabolism of the urea cycle with an incidence of 1 in 14 000 live births.
- Pregnancy in women with inherited metabolic diseases are becoming more common due to an improved medical care and newborn screening.
- Pregnancy and the puerperium in particular can be a challenging time in women with OTC deficiency due to potentially fatal hyperammonemic crises.
- Preconceptual counselling and prenatal diagnosis should be offered to all women known to be suffering from an OTC mutation.
- Multidisciplinary management is essential and treatment includes the avoidance of triggers, a low-protein diet, medication to aid the excretion of ammonia and a comprehensive management plan.

Competing interests None.

Patient consent Obtained.

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