

Obstetric implications of being an ornithine transcarbamylase (OTC) deficiency carrier - a case series

A case series looking at two cases and the successful obstetric management of the rare metabolic disorder OTC deficiency, at York hospital in March 2022.

Introduction	Objective
Ornithine Transcarbamylase deficiency is an X-linked with variable phenotypic expression in females who carry the disease. Ornithine transcarbamylase is one of six enzymes in the urea cycle, a process which converts ammonia into urea (1).	This case series of two women with heterozygous OTC (Ornithine transcarbamylase) deficiency who had successful deliveries in March 2022 at York hospital. Managing this very rare metabolic disorder is complex and involves input from a wider MDT.
Case 1	Case 2
31-year-old lady, P2G5, who has heterozygous OTC deficiency, who successfully delivered a female baby in March 2022. She has a 5-year-old daughter who is an asymptomatic OTC carrier and sadly had a neonatal death of her son at 4-days postpartum. In this pregnancy she had a NIPT which revealed she was carrying a female fetus. She declined further invasive testing of her fetus. On postnatal testing her daughter was found to have heterozygous OTC deficiency.	29-year-old lady, P2G7, who has heterozygous OTC deficiency, who successfully delivered a male baby in March 2022. She has a 4-year-old son who was diagnosed OTC deficiency presenting with hyperammonaemia neonatally and had a successful liver transplant at 6 months old. In this pregnancy she had a NIPT which revealed she was carrying a male fetus. She underwent invasive testing with a CVS which revealed that the pregnancy had not inherited the OTC gene alteration.

Key drugs - to aid excretion of nitrogen
- Sodium benzoate - Forms hippurate which is excreted in the urine - Sodium phenylbutyrate - Forms phenylacetylglutamine which is excreted in the urine - L-Arginine - To replace arginine which cannot be synthesised in the urea cycle
The drugs should be made up in 10% glucose in either a 50 ml syringe or 500 ml bag (maximum concentration 2.5g in 50mls or 25 g in 500 ml bag) and given by a syringe pump or by an infusion pump (2). These drugs are only to be given for immediate emergency management prior to seeking advice from the local metabolic disease centre.
See BIMDG (British Inherited Metabolic Disease Group) guidelines for exact doses and infusion rates (3) (4).

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Obstetric management plan for OTC deficiency carriers

In order to aid with the management of this rare metabolic disorder during pregnancy, a management plan has been created with input from specialists in: obstetrics; anaesthetics; metabolic disease; and dieticians. In addition, further input and advice around the management of the above cases was made with paediatricians and geneticists.

Antenatal care

- Serial fetal growth scans
- Monthly ammonia levels
- MDT management plan alongside Metabolic disease centre
- Amino acid profile to be done at metabolic disease centre
- Vitamin replacement (Solvazinc 1 tablet BD, Vitamin B12 replacement, Vitamin D replacement)
- Paediatrics referral
- CT head and ophthalmology review to assess for raised ICP.

Intrapartum care

- Prepare key drugs (see key drugs and BIMDG guidelines)
- Consider epidural in the first stage of labour to blunt the stress response (avoid if raised ICP)
- Avoid exhaustion and prolonged labour. Avoid a prolonged second stage, can have a passive 1 hour second stage but active second stage should be limited to 1 hour with instrumental delivery considered after 1 hour of active second stage.
- Maintain 2000kcal of protein free calories.
- For Caesarean sections patients should take their usual medicines orally until the point of fasting. Once fasting IV 10% dextrose +/- electrolytes should be started at 125mls/hr pre- and post-partum until oral intake is satisfactory.
- Caesarean section can be performed under epidural, spinal or GA, but raised ICP must be excluded.
- Cord bloods should be taken with a genetic request form to check the baby's OTC gene variant status.

Postnatal care plan

- Baby needs to transfer to neonatal unit immediately after birth.
- Maternal plasma amino acids, ammonia, urea, electrolytes, and acid-base should be checked at 4 hours, then 12 hours post-partum, then daily for 14 days. The ammonia levels should be closely monitored and if >50 the metabolic disease centre should be contacted for advice.
- Maternal vegetarian diet for the first week post-partum. If ammonia levels are well controlled, meat can be reintroduced.
- Decompensations are most likely to occur between day 3 and day 12 post-partum and patients should be monitored closely for signs of encephalopathy.
- Patients can breastfeed, but breastfeeding does increase the risk of catabolism and therefore acute metabolic decompensation and hyperammonaemia post-partum.

Signs of ammonia toxicity

Signs can be subtle and difficult to assess, especially early in decompensation. Signs are generally neuro-psychiatric. Initial presentations include lethargy, vomiting, loss of appetite, irritability, agitation and seizures. With more severe decompensation this can lead to delirium, hallucinations, ataxia and fluctuating consciousness (5).

Discussion

As ornithine transcarbamylase is one of the enzymes in the urea cycle, a deficiency can lead to difficulty in the conversion of ammonia into urea. Ammonia is created from excess protein intake or catabolism and can be toxic. With this enzyme deficiency, ammonia levels can build up leading to hyperammonaemia and encephalopathy. A careful balance needs to be met between minimising the risk of fetal growth restriction due to amino acid deficiencies versus the risk of maternal acute metabolic decompensation due to excess protein consumption. In addition, monitoring for catabolism is key, closely monitoring ammonia levels to assess for a catabolic state, and ensuring stressors such as fasting, infection, or surgery, are minimised where possible.

Important antenatal considerations include the diagnosis of OTC deficiency in the fetus. This is often initially done through non-invasive prenatal testing (NIPT) to assess the gender of the fetus. As the disorder is X-linked an affected male is likely to suffer from severe symptoms, unlike carrier females, who usually experience more mild symptoms. If a fetus is revealed to be male, counselling should be offered for consideration of invasive testing.

Conclusions

Pregnant patients with OTC deficiency have a significant risk of neurological complications and adverse fetal outcomes if not managed appropriately. Antenatal, intrapartum, and postnatal management plans have been made in conjunction with metabolic disease specialists and the MDT to minimise these risks. Education of medical professionals involved in care of patients who are OTC deficiency carriers is key to improving understanding and management of this disease.

References

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