Urea cycle disorders: a life-threatening yet treatable cause of metabolic encephalopathy in adults

Nicholas F Blair,1 Philip D Cremer,1 Michel C Tchan2

1Department of Neurology, Royal North Shore Hospital, Sydney, Australia
2Adult Genetic Metabolic Disorders Service, Westmead Hospital, Sydney, Australia

Correspondence to
Dr Michel C Tchan, Department of Genetic Medicine, Westmead Hospital, Hawkesbury Road, Westmead NSW 2145, Australia; michel.tchan@health.nsw.gov.au

Accepted 24 June 2014
Published Online First 14 August 2014

ABSTRACT

Urea cycle disorders are inborn errors of metabolism that, in rare cases, can present for the first time in adulthood. We report a perplexing presentation in a woman 4 days postpartum of bizarre and out-of-character behaviour interspersed with periods of complete normality. Without any focal neurological signs or abnormality on initial investigations, the diagnosis became clear with the finding of a significantly elevated plasma ammonia level, just as she began to deteriorate rapidly. She improved following intravenous dextrose and lipid emulsion, together with sodium benzoate, arginine and a protein-restricted diet. She remains well 12 months later with no permanent sequelae. Whilst this is a rare presentation of an uncommon disease, it is a treatable disorder and its early diagnosis can prevent a fatal outcome.

CASE REPORT

A 38-year-old woman presented 5 days postpartum with an acute onset behavioural disturbance. She had been primigravid with an uncomplicated antenatal period other than breech presentation, requiring delivery by caesarean section. She had vomited twice the day before, but was otherwise well. During the night her husband woke to find her confused. She asked how he had entered the house and repeatedly told him to get out. She appeared to mistake her husband for his brother, and could not recall her recent childbirth. She became uncharacteristically aggressive and violent, and an ambulance was called.

On arrival in hospital, she was disoriented, markedly agitated and unable to follow commands. There was no meningism or focal neurological signs. She was afebrile and the remainder of examination was normal. There was no significant past medical history. She was taking no regular medications other than analgesics for postoperative pain. She had no previous mood disorder or other psychiatric condition. There was no recent alcohol intake or history of substance abuse.

Her initial blood results showed multiple mild abnormalities (table 1), many of which could be explained by recent pregnancy; in particular, there was no renal or hepatic dysfunction, other than mildly elevated serum alkaline phosphatase, which may have been due to placental production. Her CT scan of head was normal. CSF protein was mildly elevated at 0.58 g/L (0.15–0.45) with normal CSF glucose and cell counts; Gram stain was negative.

By the next morning, her clinical status had completely normalised. Detailed neurological and psychiatric assessments were normal. In the absence of any alternative explanation, a provisional diagnosis of post-partum psychosis was made, although further investigations were awaited. Later that evening, her behavioural state relapsed. She became disoriented with fluctuating responses to cognitive tasks and profound amnesia for recent events. She had marked verbal and motor perseveration. On asking her to stand from a chair, for example, she performed this task repetitively until stopped. The remaining examination was normal, apart from subtle asterixis.

Her MR scan of brain was normal. Her EEG showed generalised delta slowing but no specific abnormality. Her plasma ammonia was significantly elevated at 292 μmol/L (normal 10–50). Shortly thereafter, she markedly deteriorated, requiring admission to the intensive care unit, with progressively declining responsiveness and prominent asterixis.

Arterial blood gas results demonstrated a respiratory alkalosis with pH 7.52 (RR 7.35–7.45), PCO2 29 mmHg (RR 32–45

mmHg) and HCO₃ 24 mmol/L (24–32 mmHg). Her repeat ammonium level was 382 μmol/L. A urea cycle disorder was considered likely and treatment was started before confirmatory results were available. She was given 10% dextrose and 20% lipid emulsion (Intralipid) infusions intravenously. Treatment with sodium benzoate and arginine was also commenced and her diet was restricted to < 5g/day of protein.

She improved over the next 24 h and, by 48 h, was alert and orientated with a serum ammonia concentration of 50 μmol/L. We continued treatment with intravenous calories, benzoate and arginine for 3 days, before changing to oral arginine. Her plasma amino acids (taken prior to treatment) revealed a low arginine and citrulline, and her urine testing showed elevated orotate, consistent with a diagnosis of ornithine transcarbamylase (OTC) deficiency. Following discharge, she needed additional oral benzoate to maintain stable ammonia levels. She remains well 12 months later.

Sequencing of all exons, including intron/exon boundaries, of the OTC gene showed no pathogenic mutation. This occurs in approximately 30% of biochemically confirmed OTC deficiency cases and is likely due to intronic or promoter mutations. The patient has one sister who was well and there was no family history of unexpected male deaths. A protein loading challenge showed that her sister was unaffected.

**DISCUSSION**

Urea cycle disorders are inborn errors of metabolism where there is a genetic defect in one of the enzymes

| Table 1 | Initial blood test results |
|-----------------|-----------------|-----------------|
| **Test**        | **Result**      | **Normal range** | **Range in pregnancy** |
| Haemoglobin (g/L) | 108 ↓        | 115–160         | 110–150 |
| White cell count (×10⁹/L) | 5.0          | 4.0–11.0        |         |
| Platelet count (×10⁹/L) | 312         | 150–400         |         |
| Serum sodium (mmol/L) | 146 ↑       | 134–145         | 132–140 |
| Serum potassium (mmol/L) | 3.3 ↓       | 3.5–5.0         | 3.2–4.6 |
| Serum chloride (mmol/L) | 108 ↑       | 97–107          | 97–109  |
| Serum bicarbonate (mmol/L) | 20 ↓      | 24–34           | 18–26   |
| Serum urea (mmol/L) | 2.7 ↓       | 3.1–8.1         | 1.0–3.8 |
| Serum creatinine (μmol/L) | 40 ↓       | 49–90           | 40–80   |
| Anion gap (mmol/L) | 22 ↑        | 7–17            | 11–18   |
| Serum albumin (g/L) | 32 ↓        | 35–46           | 24–31   |
| Serum bilirubin (μmol/L) | 3 ↓         | 3–18            |         |
| Serum alkaline phosphatase (U/L) | 161 ↑    | 41–119          | 125–250 |
| Serum γ glutamyl transferase (U/L) | 9 ↑        | 5–65            |         |
| Serum alanineaminotransferase (U/L) | 40 ↑       | 5–40            |         |
| Serum aspartateaminotransferase (U/L) | 36 ↑       | 12–36           |         |

References ranges for pregnancy are given for results that were outside of the routine reference ranges.

**Figure 1** The urea cycle produces urea from the nitrogenous waste products of protein metabolism. The six enzymes of the pathway are numbered 1–6, with their associated gene in brackets.

of the urea cycle, which is responsible for the metabolism of nitrogen waste from the breakdown of proteins (figure 1). In doing so, the cycle produces urea as a by-product. It may be necessary to replace arginine and/or citrulline, depending on which -asparaginase may also precipitate a hyperammonaemic crisis. As in this case, women with OTC deficiency are at risk of decompensation during the post-partum period, due to the increased catabolic protein load following involution of the uterus.

In an adult presenting with acute encephalopathy, there may be no other suggestion in the clinical assessment that the condition might be related to a genetic metabolic disorder, highlighting the importance of plasma ammonia testing, even when there is no evidence of hepatic or renal dysfunction. In adults, a plasma ammonia >80 μmol/L, in the absence of renal or hepatic dysfunction, should raise suspicion of a urea cycle defect. Plasma amino acid and urine organic acid tests are used to distinguish the different urea cycle disorders (table 2).

OTC deficiency is the most common form of urea cycle disorder (55%). Unlike other urea cycle disorders, which are recessive, its inheritance is X linked. Men classically have an infantile-onset, severe form. Female heterozygotes are not always asymptomatic. Female heterozygotes are not always asymptomatic with 15% developing symptoms. Women show considerable variation in clinical symptoms from minimally symptomatic illness to recurrent, severe hyperammonaemic coma and death.

The principles of management of urea cycle disorders are to remove excess ammonia and prevent its production from protein metabolism. In the emergent setting, the fastest way to reduce ammonia levels is to use haemodialysis. Pharmacological strategies include the use of the nitrogen-scavenging agents, sodium phenylacetate and sodium benzoate, which provide alternative pathways for nitrogen disposal. Conjugation with ammonia occurs in the liver and is then excreted by the kidneys. The use of these drugs has been associated with a survival rate of 84% in a large observational study over 25 years, a dramatic improvement on the high infant mortality rates of historical cohorts.

Defects of some urea cycle enzymes also result in deficiency of amino acids that would be generated as a by-product. It may be necessary to replace arginine and/or citrulline, depending on which
enzymes are affected. It is essential to avoid a catabolic state, particularly in the acute setting. This requires caloric supplementation with glucose, fats and amino acids. Dietary restriction of protein is an important aspect of management; however, this must be done judiciously to avoid induction of catabolism by an excessively low protein intake. Patients with severe forms of urea cycle disorders may ultimately require liver transplantation to prevent recurrent hyperammonaemic crises.

Practice points

▸ Urea cycle disorders are a rare but important cause of acute encephalopathy and can present for the first time in adulthood.
▸ It is essential that adult neurologists be aware of this condition as it is readily treatable, but can be fatal if undiagnosed and untreated.
▸ Plasma ammonia level should be a routine investigation for metabolic encephalopathy.
▸ A plasma ammonia level >80 μmol/L in a patient without renal or hepatic dysfunction should raise suspicion of the presence of a urea cycle defect.
▸ If a urea cycle disorder is suspected, diagnostic samples should be sent urgently and treatment, guided by a metabolic specialist, should be instituted prior to the diagnosis being confirmed. Crisis samples are critical for making the diagnosis and close liaison with laboratory personnel is important to ensure prioritisation and appropriate additional testing is undertaken.

Contributors NFB, PDC and MCT were involved in the clinical care of the patient. NFB wrote the first draft. The manuscript was critically reviewed and substantial revisions contributed by PDC and MCT.

Competing interests None.
Patient consent Obtained.
Provenance and peer review Not commissioned; externally peer reviewed. This paper was reviewed by Duncan Cole, Cardiff, UK.

REFERENCES