

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

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## 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 disorientated, 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 disorientated 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  $\mu\text{mol/L}$  (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), pCO<sub>2</sub> 29 mmHg (RR 32–45



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**Table 1** Initial blood test results

Test	Result	Normal range	Range in pregnancy
Haemoglobin (g/L)	108 ↓	115–160	110–150
White cell count ( $\times 10^9/L$ )	5.0	4.0–11.0	
Platelet count ( $\times 10^9/L$ )	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 ( $\mu\text{mol/L}$ )	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 ( $\mu\text{mol/L}$ )	3	3–18	
Serum alkaline phosphatase (U/L)	161 ↑	41–119	125–250
Serum $\gamma$ glutamyl transferase (U/L)	9	5–65	
Serum alanine aminotransferase (U/L)	40	5–40	
Serum aspartate aminotransferase (U/L)	36	12–36	

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

mmHg) and  $\text{HCO}_3^-$  24 mmol/L (24–32 mmHg). Her repeat ammonium level was 382  $\mu\text{mol/L}$ . A urea cycle disorder was considered likely and treatment was started

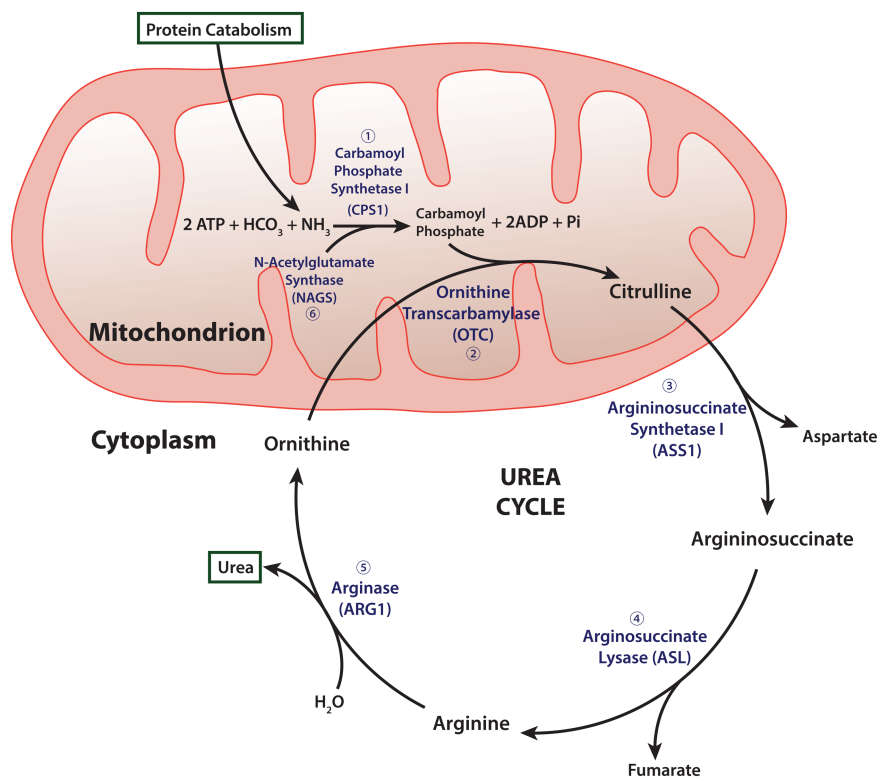
before confirmatory results were available. She was given 10% dextrose and 20% lipid emulsion (Intralipid) infusions intravenously. Treatment with sodium benzoate and arginine was also commenced and her diet was restricted to < 5g/day of protein.

She improved over the next 24 h and, by 48 h, was alert and orientated with a serum ammonia concentration of 50  $\mu\text{mol/L}$ . 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<sup>1</sup> 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



**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.

**Table 2** Urea cycle disorders and expected investigation results

Urea cycle disorder	Gene	Inheritance	Plasma amino acids	Urine organic acids
Carbamoylphosphate synthetase I deficiency	CPS1	Autosomal recessive	↓ Arginine ↓ Citrulline	↓/Normal urinary orotic acid
Ornithine transcarbamylase deficiency	OTC	X linked	↓ Arginine ↓ Citrulline	↑ Urinary orotic acid
Argininosuccinic acid synthase deficiency or citrullinaemia type I	ASS1	Autosomal recessive	↑ Arginine ↑ Citrulline	
Argininosuccinase acid lyase deficiency or argininosuccinaciduria	ASL	Autosomal recessive	↑ Arginine ↑ Citrulline	
Arginase deficiency	ARG1	Autosomal recessive	↑↑ Arginine	
N-acetylglutamate synthase deficiency	NAGS	Autosomal recessive	↓ Arginine ↓ Citrulline	↓/Normal urinary orotic acid

Plasma amino acid and urinary organic acid levels indicated as being low (↓) or high (↑) relative to the reference range.

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 from ammonia. The urea cycle is also the only endogenous source of the amino acids arginine, ornithine and citrulline. In humans, this biochemical pathway occurs primarily in the liver, but to a lesser extent in the kidney. The incidence of urea cycle disorders is about 1:35 000 live births.<sup>2</sup>

Classically, urea cycle disorders present in the neonatal period with vomiting, anorexia and lethargy that rapidly progresses to encephalopathy, coma and death if untreated. Plasma ammonia of greater than 1000 µmol/L may be found in these circumstances and results from a severe deficiency or total absence of any of the first four enzymes in the urea cycle (CPS1, OTC, ASS, ASL) or the cofactor NAGS. In cases where there is only a partial deficiency of these enzymes, or in arginase deficiency, the symptoms may be mild or not develop until adulthood. As recognition of these disorders has improved, it has emerged that only a third of patients present in the neonatal period, with the majority in childhood, but less than 10% over the age of 16.<sup>3</sup>

In adults, symptoms of this disorder may include intellectual impairment, nausea, vomiting, headaches, ataxia, protein intolerance, psychiatric disease and encephalopathy. In rare cases, other focal neurological signs may occur. Respiratory alkalosis is a common early finding caused by hyperventilation secondary to the effect of hyperammonaemia on the brainstem. However, the first sign may be an acute life-threatening encephalopathy. We are aware of a similar case at another hospital, where the diagnosis of a urea cycle disorder was not recognised, with a fatal outcome. Indeed, in several reported adult cases the initial presentation was fatal.<sup>4–6</sup>

In adult cases presenting in acute metabolic crisis, there is often an identifiable precipitant such as an increased protein load, or physiological stress such as an intercurrent illness or surgery. Medications including valproate, salicylates, corticosteroids and

L-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,<sup>7</sup> 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%).<sup>3</sup> 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 with 15% developing symptoms. Women show considerable variation in clinical symptoms from minimally symptomatic illness to recurrent, severe hyperammonaemic coma and death.<sup>8</sup>

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,<sup>9</sup> 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.<sup>10</sup> 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.

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