Late-onset ornithine transcarbamylase deficiency: a potentially fatal yet treatable cause of coma

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Coma is a common presentation to hospital. In most cases, routine history or investigations reveal the diagnosis. Rarely, a patient remains comatose for no obvious reason. Here we describe such a case, where thinking beyond the usual diagnostic possibilities and extrapolating therapeutic principles from other areas of medicine prevented rapid progression to death.

Clinical record

A 39-year-old woman who was 12 weeks' pregnant was admitted to the neurology ward to investigate a 1-day history of confusion and fluctuating level of consciousness. She had experienced daily hyperemesis over the previous 3 weeks, but there had been no associated headache, fever or other constitutional symptoms. She had not commenced any new medications. Her husband reported a similar episode 8 years previously, shortly after the birth of her first child. At that time, she was readmitted to the maternity hospital with a differential diagnosis of postpartum psychosis or an ill-defined organic disease. Her symptoms resolved spontaneously over 5 days. Computed tomography and lumbar puncture gave normal results, and she discharged herself before undergoing magnetic resonance imaging (MRI) or electroencephalography (EEG).

Examination revealed a haemodynamically stable patient with a Glasgow Coma Score (GCS) of 10 (E2 V3 M5). Pupillary reactions were normal, corneal and vestibulo-ocular reflexes were intact, and fundoscopy revealed normal optic discs. There was no facial weakness, and the gag reflex was present. There was withdrawal to pain in all four limbs. Deep tendon reflexes were intact, and plantar reflexes were bilaterally flexor. MRI of the brain showed non-specific deep white matter T2 hyperintensities, with no evidence of cerebral oedema or venous sinus thrombosis. EEG showed generalised rhythmic delta activity consistent with encephalopathy. Her level of consciousness did not improve, and although she did not require intubation, she was transferred to the intensive care unit for observation.

Initial biochemical investigations showed a low serum urea concentration, raised bilirubin concentration and respiratory alkalosis. The erythrocyte sedimentation rate, C-reactive protein concentration and full blood count were unremarkable. A lumbar puncture showed a normal opening pressure, acellular fluid and normal biochemistry profile. Ultrasound examination confirmed the presence of a single viable fetus, with biometry findings consistent with the estimated gestational age.

Given the EEG findings, the treating neurology team suspected a metabolic cause of encephalopathy and requested measurement of the serum ammonia level. This was found to be 288 μmol/L (reference range, 11–35 μmol/L), confirmed on repeat testing. Sodium valproate toxicity and paracetamol overdose are the most common causes of drug-induced hyperammonaemia, but neither drug was detectable. In the absence of obvious liver dysfunction and drug causes, a urea cycle disorder was considered. On the suggestion of the hepatology team, we sought the advice of the metabolic unit at the Royal Children's Hospital, Melbourne. The urinary and plasma amino acid profile was found to be consistent with ornithine transcarbamylase (OTC) deficiency (Table 1).

Based on the history and ammonia level, before confirmation of the diagnosis, the metabolic physician advised beginning treatment for OTC deficiency using sodium benzoate (2 g bolus every 6 h). To further reduce the plasma ammonia concentration and to halt protein catabolism, parenteral dextrose (25%, 20 mL/h) and Intralipid (Baxter) (30%, 250 mL over 6 h) were recommended. From our experience in managing hyperammonaemia of other aetiol-

ABSTRACT

Hyperammonaemia due to ornithine transcarbamylase (OTC) deficiency is a well-described cause of coma in neonates. Rarely, adults with this disorder may also present with coma. Here we describe the first reported case, to our knowledge, in a pregnant woman. She was successfully treated with metabolic therapy and, contrary to usual paediatric practice, renal replacement therapy. We review the biochemistry of OTC deficiency and other urea cycle disorders, and discuss the physiological rationale and evidence base for treatment of this condition. We highlight the need to consider hyperammonaemia in the differential diagnosis of coma.

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ogy in adults, combined with the results of an urgent literature review, we commenced continuous venovenous haemodiafiltration (CVVHDF) with high-volume (4 L) exchanges.

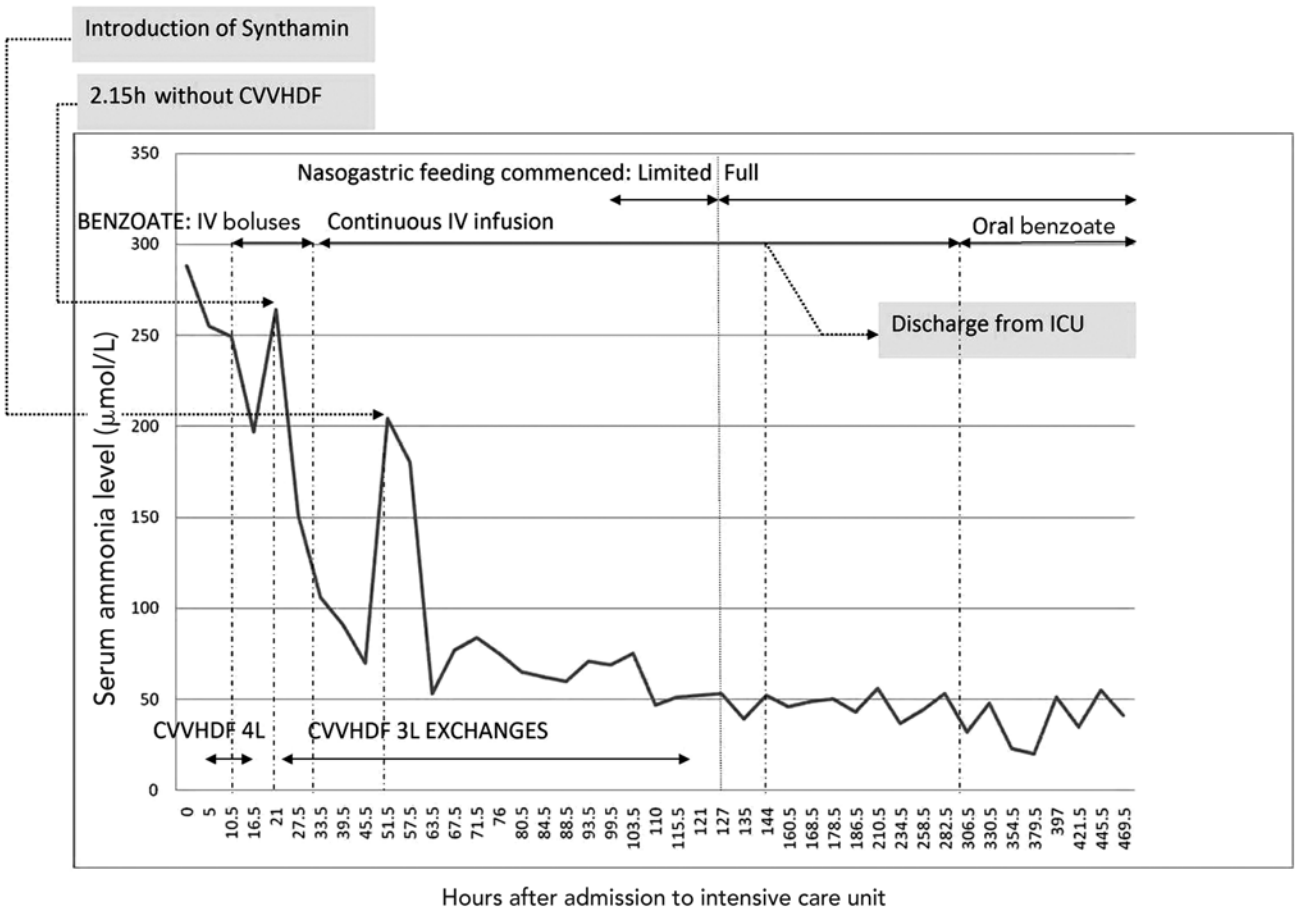
Table 1. Plasma amino acid and urinary orotic acid concentrations in the patient on Day 1

Variable	Result	Reference range
Plasma amino acid (μmol/L)		
Alanine	136	205–496
Arginine	33	53–115
Citrulline	6	23–49
Glutamine	1286	520–742
Ornithine	14	32–88
Phenylalanine	28	37–61
Valine	131	151–302
Urinary orotic acid (μmol/mmol creatinine)	73.5	< 4.9

Over the next 12 hours, the patient's ammonia level decreased, and her level of consciousness increased to a GCS of 14. Sodium benzoate was changed to a continuous infusion (0.5 g/kg per 24 h), and intravenous arginine (0.5 g/kg per 24 h) was added. The ammonia level decreased steadily apart from two fluctuations (Figure 1). The first occurred on Day 2 after a brief interruption to CVVHDF, and the second on Day 3 following the addition of parenteral protein (Synthamin 17 [Baxter], 0.3 g/kg) as a slow infusion over 4 hours, as is our usual practice for nutritional supplementation. Neither increase in ammonia level was associated with notable clinical deterioration. Indeed, by the end of Day 3, the patient was able to talk with her family who remarked that she was almost her usual self.

On Day 4, the parenteral protein dose was increased to 0.5 g/kg, administered by continuous infusion over 24 hours to avoid increasing ammonia level, as had occurred with the 4-hour infusion on Day 3. On Day 5, enteral feeds were introduced at 35 mL/h, containing 0.8 g/kg protein (8 MJ total energy/day, including carbohydrate and fats).

Figure 1. Serum ammonia concentration in the patient over time after intensive care unit admission



CVVHDF = continuous venovenous haemodiafiltration.

The following day, the target rate of 105 mL/h was achieved, so parenteral nutrition was ceased. Renal replacement therapy (RRT) was also discontinued.

On Day 7, the patient returned to the ward, where nasogastric feeding was continued. Oral feeding was gradually introduced, including tablets of sodium benzoate (200 mg/kg per day) and citrulline (250 mg/kg per day, replacing arginine). On Day 21, she was discharged from hospital on a low-protein diet, with arrangements for dietary follow-up and ongoing management in the metabolic unit at the Royal Children's Hospital.

The patient was subsequently reviewed by the perinatal genetics team. Retrospectively, she reported a history of meat intolerance and the death of both a male sibling at 3 days of age and the son of a maternal aunt, consistent with X-linked inheritance. OTC gene testing was successful, and prenatal diagnosis was offered. Chorionic villus sampling at 14 weeks' gestation confirmed the fetus to have a normal female karyotype. Subsequent gene testing confirmed the fetus was not a carrier of OTC deficiency. Carrier testing of other family members is ongoing.

Table 2. Causes of hyperammonaemia

Overproduction of ammonia	Reduced elimination
Protein load	**Liver failure**
• Gastrointestinal haemorrhage	• Acute or chronic
• Gastric bypass	**Drugs**
• Multiple myeloma	• Valproate
• Allogeneic stem cell transplantation	• Carbamazepine
• Parenteral nutrition	• Aspirin
Increased catabolism	• Rifampicin
• Starvation	**Metabolic errors**
• Seizures	• Urea cycle disorders
• Vigorous exercise	• Organic acidaemias
• Burns	• Fatty acid oxidation disorders
• Corticosteroids	
Urinary	
• Urease-producing infection (eg, *Proteus* and *Klebsiella* spp.)	
• Congenital ureteric obstruction associated with infection	

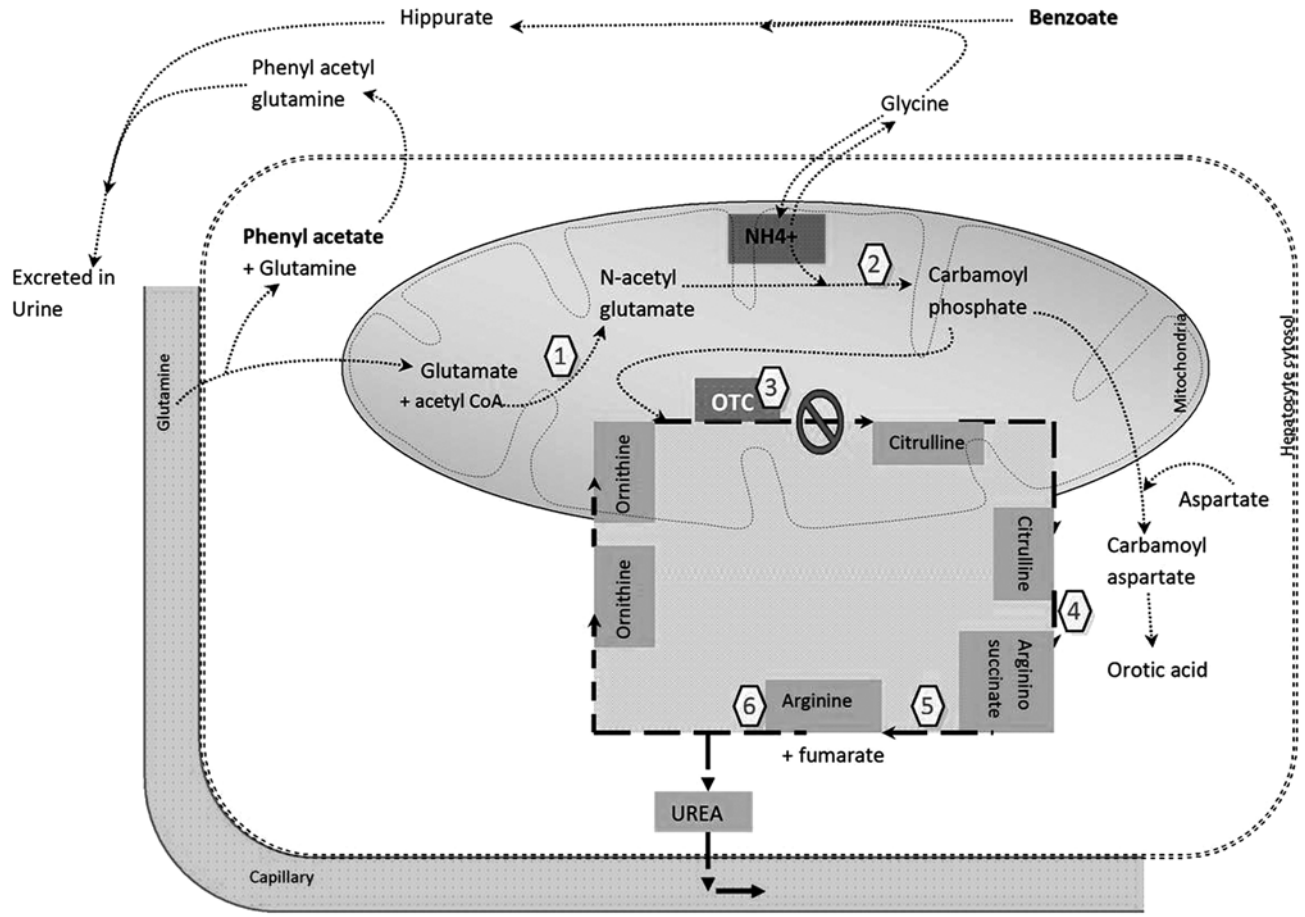
Discussion

Hyperammonaemia caused by a urea cycle disorder is a rare cause of metabolic encephalopathy that, if untreated, can lead to cerebral oedema and death.[1] Hyperammonaemia may be under-recognised by ICU clinicians given its absence from a list of causes of metabolic encephalopathy in a highly regarded textbook[2] and a recent review.[3] Ammonia accumulation is a well-known consequence of liver failure that contributes to hepatic coma, but there are numerous other causes of hyperammonaemia (Table 2). An acute increase in ammonia concentration (> 200 μmol/L) can produce cerebral oedema as the enzyme glutamine synthetase in astrocytes converts excess ammonia and glutamate back to glutamine, an intracellular osmolyte.[1] Ammonia is produced from the hepatic metabolism of amino acids. The main pathway of ammonia degradation is the urea cycle,[4] which is disrupted in OTC deficiency, leading to ammonia accumulation (Figure 2[5,6]). Quantitative amino acid testing in the setting of hyperammonaemia is essentially diagnostic.

Estimates of the incidence of urea cycle disorders vary, but the experience of the largest treatment centre in the United States suggests it is 1 in 8200, with OTC deficiency the most common subtype at 1 in 14 000.[7] Unlike other urea cycle disorders, OTC deficiency has an X-linked inheritance, so most affected individuals are hemizygous males lacking a second normal gene.[8] These patients usually present in the neonatal period with catastrophic hyperammonaemia if they have a null mutation, or later in childhood if they have partial enzyme activity.[9] Late-onset OTC deficiency is extremely rare in male patients,[1] but up to 15% of female carriers may become symptomatic at some time in their lives.[8] There is a wide range of phenotypic variability, from apparent normality to profound neurological impairment.[10] This is assumed to be due to variable levels of residual enzyme activity and X inactivation (Lyonisation) in hepatocytes.

We conducted a systematic review of the literature on OTC deficiency and hyperammonaemia in the adult population. We searched EMBASE and Ovid MEDLINE using the terms "ornithine transcarbamylase", "hyperammonaemia" and "treatment" and identified relevant articles by reading the abstracts and hand-searching the bibliographies of included articles. The search yielded 156 articles, of which 49 were relevant, including 26 case reports. These included three case series in adults, the largest by Maestri et al,[11] who conducted a retrospective analysis of carrier females with regard to their phenotype compared with non-carriers. Their findings confirmed anecdotal reports of voluntary protein restriction in these patients, as mutation carriers excreted significantly less urea nitrogen and total nitrogen than non-carriers. The authors concurred with the long-standing hypothesis that these patients are prone to hyperammonaemic encephalopathy when there is increased demand for protein catabolism. This may include high protein intake,[12] major surgery,[13,14] febrile illness[15-17] and corticosteroid use.[18] Parturition is also described as a precipitant, possibly because of the metabolic challenge of uterine involution. There are several reports of presentation with postpartum seizures or coma.[19-21]

Figure 2. Urea cycle and alternative pathways involved in nitrogen excretion



Key: NH_4^+ = ammonium. Enzymes involved in the urea cycle: 1 = N-acetylglutamate synthase. 2 = carbamoyl phosphate synthase. 3 = ornithine transcarbamylase (OTC). 4 = argininosuccinate synthetase. 5 = argininosuccinate lyase. 6 = arginase. (Modified from Legras et al[5] and Nelson and Cox.[6])

To our knowledge, our patient represents the first reported case of coma due to OTC deficiency in early pregnancy. The patient had suffered the catabolic stress of marked hyperemesis and anorexia before presentation. The episode after her previous pregnancy was almost certainly a manifestation of this condition but, as it was less severe and self-limiting, eluded diagnosis. A psychiatric evaluation at that time recorded that the patient was described by her family as an "academic underachiever". Long-term follow-up of girls with OTC deficiency has documented a trend towards lower intelligence.[22]

The management of our patient was challenging because of a lack of experience in managing a congenital metabolic defect presenting in adulthood. The metabolic unit of the Royal Children's Hospital provided helpful advice. In infants, the aim is to halt protein catabolism and to administer nitrogen-scavenging medication. To reverse the catabolic state, we began parenteral administration of Intralipid and carbohydrate with no additional protein in lieu of enteral feeding, to allow precise control of nutrition.

Alternative pathway treatment was first proposed by Brusilow and colleagues in 1979 as a way of increasing nitrogen excretion without involving the urea cycle,[23] and has been the cornerstone of management of urea cycle disorders since then. Phenylacetate and benzoate conjugate the amino acids glutamine and glycine to form phenylacetylglutamine and N-benzoylglycine (hippurate), respectively,[24] which are excreted in the urine (Figure 2). In Australia, only sodium benzoate is available for intravenous administration, through the Special Access Scheme, requiring consent to administer. Intravenous arginine was also commenced to replace the arginine not being produced by the deficient urea cycle.[25]

Although alternative pathway treatment is widely used, the evidence base for this practice was confined until recently to small single-centre case series.[26,27] In 2007, Enns and colleagues[28] published results of a 25-year uncontrolled, open-label, multicentre study of alternative pathway treatment (in conjunction with other therapies) for 1181 episodes of acute hyperammonaemia in 299 patients with urea cycle disorders. They reported a 96% hospital survival rate for patients with hyperammonaemia and an 84% overall survival rate, which is significantly better than survival of historical control subjects. Although most reported patients were children, an unspecified number of adults were also included.

We carefully considered the use of RRT in our patient. The paediatric team asserted that this therapy is rarely used in treating infants with urea cycle disorders, stemming from the greater technical difficulty of performing RRT in neonates and concern that dialysis clears the alternative pathway drugs that effect nitrogen clearance. Despite these concerns, we chose to begin CVVHDF, for a number of reasons. Ammonia is a smaller molecule than urea and thus readily dialysable.[29] We previously observed the rapid recovery of patients with hyperammonaemia caused by sodium valproate overdose when treated with RRT. We also noted the case report by Legras et al,[5] which described haemodialysis as an effective therapy for hyperammonaemia in this setting. In 1979, Donn et al[30] demonstrated the efficacy of haemodialysis in clearing ammonia in symptomatic OTC deficiency, with a clearance of 12 600 μg per hour, far superior to that obtained with peritoneal dialysis or exchange transfusion. This finding was replicated by others.[31,32] Although continuous venovenous haemofiltration (CVVH) was used in a number of cases,[33-36] three other reports demonstrated superior ammonia clearance with CVVHDF compared with CVVH.[37-39]

The decision to use RRT was vindicated as treatment progressed. As shown in Figure 1, RRT began at about 19:30 on the evening of admission, and serum ammonia level fell continuously thereafter except for two transient increases. As in the patient described by Legras et al, the first of these was associated with brief cessation of CVVHDF. The ammonia level rebounded despite the continuous infusion of sodium benzoate, suggesting that CVVHDF was clearing ammonia much more rapidly than alternative pathway therapy alone would have done. Indeed, Batshaw et al[40] in a 2001 review of 20 years of alternative pathway therapy suggested that, in hyperammonaemic coma (ammonia > 250 μmol/L), benzoate and/or phenylacetate treatment alone is insufficient. Stoichiometrically, each mole of benzoate/phenylacetate can remove only 1 mole of nitrogen, and the quantity needed to clear large amounts of nitrogen cannot be administered because of toxicity.

However, uncertainty over the role of RRT in paediatric practice persists. Enns et al reported in 2007 that only 12% of hyperammonaemic episodes were treated with RRT, with most patients' ammonia levels normalising with phenylacetate/benzoate treatment.[28] They suggested that RRT be instituted if hyperammonaemia persists after 8 hours of alternative pathway treatment, concluding that "timely administration of alternative-pathway therapy may reduce or eliminate the need for hemodialysis", but "prospective, multicenter trials involving patients of all ages are needed to address the role of hemodialysis further".[28]

Conclusions

Our patient illustrates the importance of measuring serum ammonia level in coma of uncertain aetiology, particularly when a metabolic cause is suspected. This test enabled early diagnosis of a potentially fatal cause of coma. Treatment was based on physiological principles and published case reports, and the abrupt increase in serum ammonia during discontinuation of CVVHDF, despite persisting infusion of benzoate, supports its role as an addition to metabolic therapy in these cases. We recommend a dual approach and emphasise to clinicians to be aware of urea cycle disorders as a cause of coma in adults.

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