CASE REPORT

Unusual cause of general malaise: a young woman with ornithine transcarbamylase deficiency

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SUMMARY

A young woman presented with general malaise in relation to the metabolic condition ornithine transcarbamylase deficiency. Her ammonia level had risen to 229 $\mu\text{mol/L}$ (normal range 0–59 $\mu\text{mol/L}$). She was treated using her emergency pack of intravenous medicines and made a complete response. We briefly discuss the need to make an urgent diagnosis, the 'mechanism' for checking serum ammonia levels and therapies.

BACKGROUND

Ornithine transcarbamylase (OTC) deficiency belongs to a class of genetic urea cycle disorders. The condition affects around 1 in 80 000 people. A recessive X-linked condition, OTC deficiency most often affects young males. Heterozygous females are usually asymptomatic, although around 15% will be symptomatic at some point in their lifetime.¹

All the urea cycle disorders may cause severe irreversible neurological complications through an elevation in serum ammonia concentration. Treatment of a patient suffering this condition is a medical emergency.

CASE PRESENTATION

A 24-year-old woman with known OTC deficiency was admitted to the emergency department with a 6-day history of gastrointestinal upset (vomiting) lethargy, general irritability and an overall sensation of 'not feeling right'.

She had been diagnosed with OTC deficiency since birth and had previously presented with multiple flares (4 admissions since 2014). Decompensation of her OTC deficiency appears to have been precipitated by episodes of diarrhoea and vomiting, causing the serum ammonia levels to rise above a normal range 0–59 $\mu\text{mol/L}$. The medical history included vestibular migraines and vertigo. There was no family history of a similar metabolic disorder.

Aside from being clinically dehydrated, clinical examination was normal with a Glasgow Coma Scale score of 15/15 and no neurological or encephalopathic features.

INVESTIGATIONS

Routine bloods and culture of urine and faeces were unremarkable. Her ammonia level had risen to 229 $\mu\text{mol/L}$ on this admission. Previous exacerbations have caused the ammonia level to reach a peak of greater than 280 $\mu\text{mol/L}$.

DIFFERENTIAL DIAGNOSIS

This was not really relevant in this case of established metabolic disorder.

TREATMENT

Initially, her fluid status was corrected with normal saline. Otherwise, treatment was aimed at reducing the production of ammonia with a low protein diet and medication that promoted the removal of nitrogen, including sodium benzoate, sodium phenylbutyrate and L-arginine (figure 1). The patient had her own emergency intravenous pack containing these required medications as she could not initially tolerate oral medications.

Once recovered, the advised low-protein diet comprised up to 40 g of natural protein per day. The avoidance of particularly protein-rich foods, including red meat and fish, is vital to maintaining a low protein intake. In addition, she was advised to increase her calorie intake to avoid a potentially catabolic state promoting ammonia production. These dietary modifications included regular use of multivitamins, including vitamin B₁₂ (as this is normally obtained from meat), to supplement her nutritional requirements.

OUTCOME AND FOLLOW-UP

Her symptoms improved following fluid resuscitation, antiemetics and treatment with rescue medications in a matter of hours. Her ammonia levels decreased to 91 $\mu\text{mol/L}$ on discharge and she was discharged once tolerating oral medication and adherent to her usual low protein diet (as expanded on in the discussion). Follow-up was arranged at her local metabolic outpatient service with the general practitioner to review ammonia levels on discharge.

DISCUSSION

OTC deficiency is caused by mutations in the OTC gene, located on the X chromosome. Although the condition itself is rare, it is thought to be the most common of the urea cycle disorders.

Defects in the OTC enzyme, located within the hepatocyte mitochondria, cause dysfunction in the urea cycle leading to nitrogen accumulation in the bloodstream in the form of ammonia. The diagnosis is made from a combination of symptoms and elevated blood ammonia levels, followed later by a more detailed genetic analysis.² Blood samples for ammonia estimates require the laboratory to be pre-warmed and the sample to be transferred on ice (ammonia concentrations can rise rapidly after venesection due to the in vitro metabolism of nitrogenous compounds and the degradation of glutamine).

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Figure 1 Schematic demonstrating the various potential therapies in urea cycle disorders.

Decompensation of this condition is often triggered by intercurrent illness, particularly gastroenteritis, fasting and any protein loading. Symptoms can be precipitated postoperatively, postpartum, following a crush injury or cancer therapies (radiotherapy or chemotherapy) and with high-dose steroids, although an obvious precipitant is not always apparent. Two medications that are most frequently implicated in causing hyperammonaemia are haloperidol and sodium valproate.^{3 4}

Ammonia is more commonly raised in other conditions, including cirrhosis and gastrointestinal bleeding. While there is some individual variability, symptoms tend to occur at levels higher than 100 $\mu\text{mol/L}$, with encephalopathic features emerging at levels of greater than 200 $\mu\text{mol/L}$ and frequent at between 500 and 1000 $\mu\text{mol/L}$.⁵ Clinical suspicion of hyperammonaemia or significantly elevated plasma ammonia levels in a patient with OTC deficiency should prompt immediate intravenous treatment. Failure to treat can lead to the development of cerebral oedema, coma and death.

Medications used in the treatment of decompensated OTC deficiency create an alternative pathway to urea for the excretion of nitrogenous waste (figure 1).^{2 6} Benzoates, such as sodium benzoate, act as a nitrogen scavenging agent, being conjugated to glycine to form hippurate, which is rapidly excreted in the urine. Phenylbutyrate is metabolised to phenylacetylglutamine, which is also excreted in the urine. Lastly, Arginine is normally synthesised in the urea cycle, but in the urea cycle disorders are usually supplemented to meet patient needs by improving the overall functioning of the urea cycle.

It is important to immediately correct dehydration, initially with 0.9% normal saline and later with 10% dextrose, the latter at a rate of 2 mL/kg/h. Other management includes treating the underlying infection and constipation. In patients presenting with encephalopathy, intensive therapy unit (ITU) referral and haemodialysis should be considered. As the patient improves clinically, oral or enteral feeds should be introduced and natural protein intake should be reintroduced gradually. OTC deficiency

does not require as strict a protein restricted diet as do other urea cycle disorders, though a diet of between 30 and 40 g of protein/day is recommended in adults. During periods of decompensation, oral protein intake should be stopped completely. Some patients are also advised to supplement their calorie intake with glucose polymer solutions at regular intervals in the day. Patients will rely on specialist dietician advice to learn how to balance quantities of allowed and weighed portions of protein in what are referred to as 'exchanges'. One 'exchange' is equivalent to 1 g of protein and patients learn how to calculate the protein exchange value of manufactured foods.

In severely affected cases, liver transplantation is considered a curative procedure.⁷

Current guidelines, including the emergency regimen and patients' own 'rescue packs', are outlined by The British Inherited Metabolic Disease Group.⁶ 'Rescue packs' for immediate use are dispensed to patients as sufficient supplies of these drugs are not quickly and easily available from hospital pharmacies. Such patients also require discussion with the local metabolic unit.

Learning points

- ▶ Patients with ornithine transcarbamylase deficiency and similar metabolic conditions producing hyperammonaemia represent a medical emergency.
- ▶ Vomiting and general malaise is a common early warning sign for rising ammonia levels in these patients.
- ▶ Blood ammonia levels require the sample to be taken to the laboratory on ice and for the laboratory to be prewarned of its arrival.
- ▶ Treatment involves the use of medications (an emergency rescue pack) that many patients will have had dispensed to them and should bring with them to hospital.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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