Learning from errors

Transient hyperammonaemia in a patient with confusion: challenges with the differential diagnosis

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Summary

Hyperammonaemia is often seen in the context of decompensated liver disease. It may also be triggered by stressful medical conditions in adults with partial enzyme deficiencies of the urea cycle. Occasionally, non-hepatic causes can result in hyperammonaemia severe enough to cause symptoms. The authors report the case of a 52-year-old Turkish woman who presented with acute-on-chronic confusion, drowsiness and lethargy. Laboratory investigations revealed hyperammonaemia which had an unclear cause. Although first thought to be secondary to a concurrent urinary tract infection, the high serum ammonia was eventually attributed to her carbamazepine. The authors recommend that doctors should include urinary tract infection and iatrogenic causes in their differential diagnosis in patients with hyperammonaemia and neurological symptoms, especially when this may be misleading in the diagnostic process.

BACKGROUND

Serum ammonia is a rarely used biochemical test and the abnormal result posed difficulties in deciding whether or not it was relevant to the clinical picture. We wrote this case report to highlight the challenge that such test posed and to highlight its relevance in a clinical setting.

CASE PRESENTATION

A 52-year-old woman presented with a 3 month history of worsening confusion and a 2 day history of acute confusion, lethargy and feeling 'off legs'. Her medical history included hydrocephalus (treated with a lumboperitoneal shunt at the age of 32), epilepsy (newly diagnosed 6 months previously), refractory hypertension, type 2 diabetes, transient ischaemic attacks and depression. Her medications included carbamazepine, lamotrigine, metformin, glimepiride, enalapril, amlodipine, bendroflumethiazide, atenolol, atorvastatin, aspirin, dipyridamol and citalopram.

On examination, she appeared confused with a Glasgow Coma Scale score of 14/15. Abdominal examination was normal with no stigmata of chronic liver disease and no focal tenderness in the suprapubic area or renal angles. She was afebrile, heart rate was regular at 72 beats per min and blood pressure was 166/93 mm Hg. Neurological examination showed reduced power and coordination in the lower limbs with exaggerated knee and ankle reflexes bilaterally. Respiratory examination was unremarkable. The nursing staff noted that the patient had increased urinary frequency. The patient mentioned a vaginal discomfort on questioning with a translator (although due to her confusion the translation was difficult to interpret).

INVESTIGATIONS

Initial investigations showed a normal full blood count except for a mild neutrophilia ($8.4 \times 10^9/l$, normal range 2.5–7.0). Serum sodium was 128 mmol/l (135–147), potassium was 3.1 mmol/l (3.4–4.9), urea 3.4 mmol/l (3.5–6.5) and

creatinine 60 $\mu\text{mol/l}$ (60–120). Liver enzymes were within reference ranges, albumin was 33 g/l (35–45) and plasma glucose was 9.3 mmol/l. In view of the hyponatraemia and hypokalaemia, bendroflumethiazide and citalopram were stopped. Her electrolytes gradually improved but she remained confused. CT of the brain showed bilateral periventricular attenuation and prominent lateral ventricles, but these findings were unchanged compared to previous CT scans that year and 4 years previously in keeping with her known history of hydrocephalus.

Lactate and ammonia were measured to exclude reversible causes of confusion. Her venous blood lactate was moderately raised at 3.9 mmol/l (0.6–2.4 mmol/l) and ammonia was 148 $\mu\text{mol/l}$ (10–47 $\mu\text{mol/l}$). Due to the increased urinary frequency, urine was sent for microscopy, culture and susceptibility testing. Microscopy revealed a white cell count of $100 \times 10^6/l$, red blood cells of $50 \times 10^6/l$ and $50 \times 10^6/l$ epithelial cells. Culture revealed $10^8/l$ enterococcus species (on the basis of colonial morphology, microscopy, Lancefield grouping and aesculin hydrolysis). The enterococcus was isolated in pure culture.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of hyperammonaemia in this case:

- ▶ Adult-onset inborn error of metabolism (a urea cycle disorder)
- ▶ Carbamazepine (case studies of hyperammonaemia secondary to carbamazepine in the literature)
- ▶ Urinary tract infection with a urea-hydrolysing organism.

TREATMENT

Her urinary tract infection was treated with nitrofurantoin for 3 days, which was changed to co-amoxiclav once antimicrobial sensitivities were known. Her carbamazepine dose was halved from 600 mg to 300 mg (but not stopped in case this precipitated a seizure). Serum ammonia 10

days later had normalised to 17 $\mu\text{mol/l}$. However, her confusional state did not return to baseline.

OUTCOME AND FOLLOW-UP

She was subsequently transferred to a tertiary centre for neurology for a suspected partially blocked lumboperitoneal shunt. Insertion of a ventriculoperitoneal shunt resulted in improvement of her symptoms.

DISCUSSION

Hyperammonaemia is a recognised cause of encephalopathy characterised by episodic confusion and coma.¹ It is usually seen in the context of decompensated liver disease where the diagnosis is relatively straightforward. However, occasionally non-hepatic causes can result in hyperammonaemia severe enough to cause confusion.²

Ammonia is a product of protein metabolism, and is required for synthesis of essential cellular compounds.³ Physiological sources of ammonia include intestinal bacteria, the purine-nucleotide cycle in skeletal muscle and other metabolic processes in the kidney and liver.³ Excess ammonia is normally excreted by the conversion to urea in the urea cycle, which requires a functional liver. Hyperammonaemia usually results from either an inability to cope with normal levels of ammonia (for example in the context of decompensated liver disease) or an inability to convert ammonia into urea (which may occur in the context of various enzyme deficiencies).

Hyperammonaemia is a serious condition associated with significant morbidity and mortality. The clinical features of hyperammonaemia are variable and often episodic. Intermittent ataxia, intellectual impairment, behavioural disturbances, epilepsy, cyclical headaches and intermittent vomiting may be presenting features. Untreated hyperammonaemia can lead to increased intracranial pressure, seizures, coma and death. If acute liver failure is not the cause of hyperammonaemia, more unusual causes of acute hyperammonaemia must be sought such as side effects of certain drugs or infections.⁴ A high index of suspicion is important if the diagnosis is not to be missed since routine investigations are often unhelpful and the measurement of serum ammonia is a key to making the diagnosis.

Non-hepatic causes of hyperammonaemia are rare but may be reversible and prompt recognition and treatment may be life saving. Urinary tract infection with urea-hydrolysing organisms is a recognised but rare cause of hyperammonaemia in the adult population.^{5 6} The urease-producing bacteria hydrolyse urinary urea to ammonium, which is converted to ammonia in alkaline pH. Since ammonia is a weak base, diffusion through the wall of the bladder to the blood is facilitated by the alkaline pH of the urine.

The high serum ammonia level in our patient in the absence of other causes such as severe liver disease, and the normalisation of blood ammonia following antibiotic treatment suggested that her hyperammonaemia was secondary to a urinary tract infection with a urea-hydrolysing organism. However, enterococci are a urease-negative

genus of bacteria and therefore would be unlikely to account for this patient's abnormal serum ammonia.

The authors therefore postulate that the hyperammonaemia was secondary to her carbamazepine. This is a rare but recognised side effect of carbamazepine with, to our knowledge, only four cases had been reported in the English literature. The mechanism by which carbamazepine causes hyperammonaemia is still unclear.⁷ In our patient, the only new medications she had started in the preceding 6 months were carbamazepine and lamotrigine for her new-onset epilepsy. It is possible that the lamotrigine was responsible for the raised serum ammonia. However, although valproate is a recognised cause of hyperammonaemia,⁷ there are no reported cases of lamotrigine-induced hyperammonaemia in the literature. We recommend that if a raised serum ammonia is found in a patient with new-onset confusion, the drug history should be carefully examined to exclude iatrogenic hyperammonaemia.

Learning points

- Hyperammonaemia is a recognised cause of encephalopathy.
- It may be caused by liver disease, certain medications, infections with urea-hydrolysing organisms and inborn errors of metabolism.
- Exclusion of the more common causes of hyperammonaemia is relatively simple and easy to achieve, by using simple biochemical and urine tests.
- Medications such as valproate and carbamazepine are recognised precipitants of hyperammonaemia and should be excluded as the cause in these patients.

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Competing interests None.

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