CASE REPORT

Multifactorial non-cirrhotic hyperammonaemic encephalopathy

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SUMMARY

A 51-year-old female presented with acute confusion associated with a non-specific headache and lethargy. The patient's history included bipolar disorder on valproate and recent travel to northern Vietnam. The patient was subsequently found to have hyperammonaemia as well as a urinary tract infection and bacteraemia with *Klebsiellapneumoniae*. The patient was presumed to have a multifactorial non-cirrhotic hyperammonaemic encephalopathy due to a combination of a urinary tract infection and bacteraemia with *K. pneumoniae*, a urease-producing bacteria, and also valproate use, a medication known to interfere with ammonia elimination. The patient's treatment included supportive care, ceasing valproate, empiric then rationalised antibiotics, N-acetylcysteine and L-carnitine. We present a case of non-cirrhotic hyperammonaemic encephalopathy and explain why it is multifactorial in origin.

BACKGROUND

Encephalopathy is a common condition resulting in admission to the intensive care unit. It is defined as altered mental state presenting as confusion, changes in behaviour or other impairments of cognition, with or without inflammation of the brain.[1] Hyperammonaemia is a common cause of encephalopathy and usually occurs in patients with liver disease. Cirrhosis is the most common cause of hyperammonaemic encephalopathy. Non-cirrhotic hyperammonaemic encephalopathy (NCHAE) is less common; however, it is increasingly being recognised as a cause of encephalopathy. Hyperammonaemia in patients in the intensive care unit is associated with high mortality, and hyperammonaemic encephalopathy can progress from confusion to coma with cerebral oedema, brain stem herniation and death.[2] We present a case highlighting that hyperammonaemia in NCHAE may be multifactorial in origin.

CASE PRESENTATION

A 51-year-old Caucasian female was brought in from home by her husband with a 1-day history of confusion associated with a non-specific headache and lethargy, 1 week after returning from a 3-week holiday in northern Vietnam. The patient had no previous episodes of confusion. Medical history included type 2 diabetes mellitus on metformin and sitagliptin, bipolar disorder stable on quetiapine, valproate and sertraline and migraines on propranolol. Examination on presentation was significant for reduced breath sounds bibasally, a Glasgow Coma Score of 13 (E3, V4 and M6) and twitching movements of all limbs but no lateralising neurology.

INVESTIGATIONS

Initial investigations showed hypoxaemia with an acute respiratory acidosis and concomitant normal anion gap metabolic acidosis (pH 7.06, pCO_2 78 mm Hg, pO_2 52 mm Hg, bicarbonate 21 mmol/L, base excess −8 mmol/L, sodium 135 mmol/L and chloride 102 mmol/L), mild neutrophilia (10.52×10^9/L, normal range 2–7.5), mildly elevated C reactive protein (25, normal <5 mg/L), an acute kidney injury (urea 12.8 mmol/L, normal range 3–8 mmol/L; creatinine 231 umol/L, normal range 45–90 umol/L), elevated transaminases (alanine aminotransferase (ALT) 600 U/L, normal <35 U/L and gamma glutamyl transpeptidase 54 U/L, normal <40 U/L) but otherwise normal liver function tests and normal coagulation profile. Plasma ammonia was elevated at 156 umol/L (normal <50 umol/L), and serum valproic acid level was 25 mg/L (therapeutic range 50–100 mg/L). Urinalysis was positive for leucocytes and leucocyte esterase. Cerebrospinal fluid (CSF) analysis showed elevated protein 0.92 g/L (normal 0.15–0.45 g/L), elevated glucose 9.2 mmol/L (however, plasma glucose was elevated at 15.5 mmol/L) but no pleocytosis (leucocyte count 3×10^6 and erythrocyte count 18×10^6). Chest X-ray showed mild pulmonary oedema, and a non-contrast brain CT showed no acute abnormality.

TREATMENT

In the emergency department, the patient failed to respond to naloxone or physostigmine for an initially suspected toxicological cause of altered consciousness. Subsequently, she was started on non-invasive ventilation, empirical antibiotics to cover for meningoencephalitis (meropenem, benzylpenicillin and aciclovir), intravenous N-acetylcysteine for an elevated ALT and regular lactulose; a urinary catheter was inserted; and she was admitted to the general high dependency unit.

Over the next 72 hours, the patient became increasingly obtunded, despite a normalised pCO_2, and she was transferred to the intensive care unit where she was intubated for airway protection. Her ALT also continued to rise, to a peak of 3820 U/L, and N-acetylcysteine was continued. Admission

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urine and blood cultures grew *Klebsiella pneumoniae*. Meropenem was continued; colistin added given her risk factors for carbapenem-resistant Klebsiella infection (recent travel to Vietnam) and her ongoing deterioration, and benzylpenicillin and aciclovir were ceased. L-carnitine, 1 g 8 hourly via nasogastric tube, was started for the persistently elevated ammonia to cover for possible valproate-induced hyperammonaemia.

Further tests on blood and CSF for viral and bacterial aetiologies, as well as anti-NMDA receptor antibodies, were negative, and abdominal imaging techniques, including a triphasic CT and an ultrasound, were unremarkable and did not show any evidence of liver pathology. A MRI brain performed on day 5 of admission showed non-specific diffuse leptomeningeal enhancement, particularly involving the parieto-occipital sulci. An electroencephalogram was requested but not performed.

OUTCOME AND FOLLOW-UP

By day 6 of her admission, she was alert without gross neurological deficit and successfully extubated. Her ammonia level returned to normal, renal function returned to baseline and ALT was down trending. The *K. pneumoniae* isolate was not carbapenem resistant, so antibiotics were rationalised to ceftriaxone and then oral amoxicillin plus clavulanate, and she was discharged home on day 11. The patient was advised to avoid sodium valproate. On follow-up, urine metabolic screen for inherited metabolic disorders was negative.

DISCUSSION

In this case, the elevated ammonia level, three times the upper limit of normal, and the absence of alternative causes of altered consciousness is indicative of hyperammonaemic encephalopathy. We propose that the hyperammonaemia was non-cirrhotic in origin and due to a combination of a urinary tract infection and bacteraemia with *K. pneumoniae*, a urease-producing bacteria, plus valproate, a medication that interferes with ammonia elimination.

Ammonia is a neurotoxic substance produced in the body through the metabolism of proteins and amino acids as well as by the actions of intestinal bacteria.[3] Under normal conditions, the majority of this ammonia is converted in the liver to the water soluble substance urea via the urea cycle.[4] Hyperammonaemia may therefore result from elevated ammonia production and/or reduced ammonia elimination.[5]

Urease-producing bacteria such as *Klebisiella* species, *Proteus mirabilis* and *Pseudomonas aeruginosa* can cause an increase in ammonia production.[4 5] Other causes of increased production include high-protein load, catabolism, haemato-oncological disorders and organ transplantation.[4 5] Urease-producing bacteria are thought to increase ammonia production by a combination of increase synthesis of urinary ammonia and urinary alkalinisation, thus increasing the percentage of ammonia in the un-ionised form, which is then able to diffuse out of the urine into the urothelial cells and then back into the systemic circulation bypassing the liver.[4] Infections due to urease-producing bacteria have been increasingly documented to cause hyperammonaemic encephalopathy, though the literature suggests that this appears to occur in association with urinary stasis and/or urinary tract anomaly, which was not evident in the described case.[6–9]

Apart from acute and chronic liver failure, decreased ammonia elimination may also be the result of medications, including valproate, carbamazepine, sulfadiazone, salicylates and glycine, as

Patient's perspective

I understand that encephalopathy is basically an altered mental state, presenting as behavioural changes, confusion and other variations of cognitive impairment. There is no doubt that, once I 'woke up' I was totally confused, full of fear and panic, unable to easily recollect what was said to me (especially in the initial stages) and, by far the worst of all, completely paranoid. On top of that, I now realise that I was also experiencing auditory and visual hallucinations – absolutely terrifying. I somehow had the belief that I was in trouble with medical staff and was therefore going to be 'kicked out' of ICU – how I ever came up with this thought, I have no idea; but unfortunately that feeling of having done something 'wrong' remained steadfastly in the foreground of my messed up mind at the time. My first months out of hospital (January – March) were a living hell. I remained totally paranoid, suspicious and 'scared to death' almost all the time. I honestly felt like I was losing my mind: Was this complete personality change going to be permanent? Was I delirious or now totally insane? Over the following months (late March – June/July), things slowly, very slowly, began to improve. At least I now understood that my hallucinations were just that – terrible things that just could not have been real. Although I feel that I am pretty much back to 'normal' now, I do still have the occasional 'flashback', however these are now few and far between. I also now understand that these issues are considered a potential consequence of my being so ill.

Surprisingly, having never been a good sleeper and prone to infinitely long periods of insomnia for all of my adult life, I now sleep like there is no tomorrow. Initially, I put this down to my ongoing recovery. In August and September, I started to have concerns: It was almost as if I was sleeping for the number of hours I would normally be awake, while being up and active for the number of hours I would normally be sleeping – a reversal of habits if you like. Adding numbers to the equation perhaps better shows the significance of this: Effectively, I was sleeping for 16–20 hours per day; being awake for only 4–8 hours in a 24 hours period. In mid-September I began making a concerted effort to have some routine in my day. I was surprised to find that it wasn't as difficult as I'd thought it would be. My endocrinologist ordered a complex metabolic screen, as well as testing my thyroid and other nutritional indices: He wanted to check that there was no physical reason for my excessive sleep. In a letter to my GP, he made mention that he wondered if it sounded more like post-traumatic stress – in which case I could then seek psychological support. I understand that recovery does involve sleep, but it is time for me to start 'living' again, considering that the fear has gone and the time is right. I do think that a major factor contributing to my excessive sleep was due to the state of shock that I was in – especially in the first 3–4 months post ICU. Now that my sleep pattern has more or less normalised, the other thing I need to start doing now is exercising.

Finally, since reading the report, I now realise just how sick I was – I was surprised that my condition took a turn for the worse after I had been admitted. I have no recall of becoming unwell, the ambulance trip, or any of my time in the ED or the HDU. As much as I've lost about two weeks' worth of time, this no longer bothers me – I don't really think I'd even want to remember any of that time anyway. I'm still here – alive and kicking – and I'm very thankful for that! I've always been terrified of hospitals, however I don't like to think how differently things would have turned out had I not gotten to SCGH when I did, and under your care and the amazing staff of the ICU.

Learning points

- It is important to measure serum ammonia in patients presenting with encephalopathy of unknown origin, even when the patient is not known to have liver disease.
- Early recognition of non-cirrhotic hyperammonaemic encephalopathy (NCHAE) can help guide treatment and potentially improve morbidity and mortality in this cohort of patients.
- When investigating a patient with NCHAE, it is important to consider more than one cause.
- Carnitine supplementation may be a useful adjunctive treatment in hyperammonaemia.

well as inborn errors of metabolism such as urea cycle disorders, congenital portosystemic shunts and ureterosigmoidostomy.[4 5] Valproate as a cause of encephalopathy with or without hyperammonaemia is well described in the literature,[5] and in adults, there does not appear to be a correlation between the valproic acid level and the development of encephalopathy.[10] There has even been a case of hyperammonaemia after a single dose of valproate in a patient who was subsequently found to have a urea cycle disorder.[11]

It has been postulated that valproate induces hyperammonaemia through several mechanisms including through its metabolism, which produces a metabolite that inhibits the first enzyme, carbamoyl phosphate synthetase I, required in the urea cycle,[4] as well as by decreasing carnitine levels through increasing the excretion of carnitine[4] and inhibition of carnitine biosynthesis.[12] Carnitine deficiency causes mitochondrial dysfunction and inhibits the urea cycle.[4] Carnitine supplementation in patients with valproate-induced encephalopathy has been shown to correlate with a more rapid reduction in plasma ammonia levels.[12] There is also some evidence to suggest that carnitine supplementation may be as effective as current standard of care, involving lactulose and oral antibiotics, in the treatment of mild to moderate hepatic encephalopathy.[13]

Like in everyday medical practice, there are a few inconsistencies and unknowns in this case. First, the cause of the elevated transaminases in this case remains uncertain, and its potential role, as a marker of liver dysfunction, in contributing to the hyperammonaemia is unclear. However, the elevated transaminases are mostly likely the result of sepsis and, of note, the abdominal imaging did not show any evidence of liver disease, and biomarkers of liver synthetic function remained largely normal throughout this patient's admission, except for an elevated international normalised ratio of 1.5 (normal range 0.9–1.3) on day 3 of her admission. Second, the leptomeningeal enhancement seen on the MRI is not consistent with the changes usually seen in hyperammonaemic encephalopathy. The MRI findings in acute hyperammonaemic encephalopathy in adults are not well described; however, the limited available literature suggests that it tends to be associated with extensive cortical injury,[14] usually with symmetrical involvement of bilateral insular and cingulate cortices.[14] The reason that these changes may not have been seen in this patient is due to the MRI being done late in the course of this patient's illness and also the prompt recognition and management of her hyperammonaemia.

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