CASE REPORT

'All that glitters is not gold': when hyperammonaemia is not from hepatic aetiology

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SUMMARY

Hyperammonaemia is often caused by decompensated liver disease. However, non-hepatic causes can sometimes result in hyperammonaemia, severe enough to cause symptoms.

We report a case of a 65-year-old man with a history of hypertension and bilateral peripelvic renal cyst who presented with acute confusion. Laboratory investigations revealed hyperammonaemia and normal liver function test. The abdominal ultrasound did not reveal any finding of liver disease or portal-systemic shunting but demonstrated bilateral peripelvic cysts with no hydronephrosis.

Hyperammonaemia was attributed to urinary tract infection with a urea-splitting *Escherichia coli* bacterium. Antibiotic therapy and lactulose were administered. His neurological status rapidly normalised over the next 48 hours, concomitantly with a decrease in ammonia level. Clinician awareness of non-hepatic causes of hyperammonaemic encephalopathy like urinary tract infection can contribute to early diagnosis and timely initiation of appropriate and potentially life-saving treatment including antimicrobial therapy, alleviating urinary obstruction, if present, and lactulose.

BACKGROUND

The occurrence of hyperammonaemia is frequently related to liver cirrhosis and, if high enough concentrations, coma and can even result in death.

Patients with symptomatic hyperammonaemia and normal liver function are diagnostic challenges for treating physicians. Possible triggers include adverse medication effects, urinary tract infections (UTIs) and late-onset enzymatic deficiencies, which might be considered in the differential diagnosis of such scenario.

This case report highlights the importance of broadening differential diagnosis in this situation to include UTI, which may cause symptomatic hyperammonaemia in spite of normal hepatic function.

CASE PRESENTATION

A 65-year-old African-American man presented to the emergency department requesting to be seen by a psychiatrist. He had disorganised thoughts and was unable to tell anything about his medical history. Based on his chief complaint, he was going to be triaged to the psychiatric crisis centre but he was noted to have a high blood pressure, so he was sent to the main emergency department.

He was unable to tell if he has a history of hypertension or if he takes any medications. His medical history retrieved from the electronic medical record showed that he had no history of liver disease, alcohol abuse or stroke. He was not on any medications and he had a history of urinary tract anomalies.

On examination, he appeared confused, with Glasgow Coma Scale of 14 E4V4M6, interacting and following instructions without difficulty. He was afebrile, heart rate was regular at 96 beats/min and blood pressure was 212/116 mm Hg. Respiratory rate was 18 breaths/min, temperature was 36.6°C and pulse oximetry was 99% on room air. Neurological examination showed no obvious asterix or focal motor deficit. He was minimally oriented to time and place, was able to recall 0 of 3 words, count backward from 100 by sevens or draw a clock face and his writing and drawing could not be assessed.

Abdominal examination was normal with no stigmata of chronic liver disease and no focal tenderness in the suprapubic area or renal angles.

Cardiovascular and respiratory system examinations were unremarkable.

Bedside bladder scan revealed postvoid residual volume of 400 mL of urine, drained with a straight catheter; however, the patient was noted to be incontinent, for which a condom catheter was placed.

INVESTIGATIONS

Initial investigations showed a normal full blood count (white blood cell $8.5 \times 10^9/L$, haemoglobin 12.3 g/dL, platelet $280 \times 10^9/L$). Serum sodium was 139 mmol/L (135–147), potassium was 4 mmol/L (3.4–4.9), urea 16 mg/dL (7–20) and creatinine 1.17 mg/dL (0.4–1.2). Liver enzymes were within reference ranges, albumin was 3.5 g/dL (3.5–4.2) and blood glucose was 107 mg/dL. Calcium was 9 mg/dL (8–10.4). Ethanol and ammonia were measured to exclude reversible causes of confusion. Ammonia was 44 $\mu\text{mol/L}$ (normal is less than 34 $\mu\text{mol/L}$) and ethanol was less than 3 mg/dL.

CT brain was normal. Urine drug screening was negative for cocaine cannabinoids and opioid metabolites. Urine microscopy revealed a white cell count of 100/high-power field (HPF), red blood cells of 20/HPF. Culture revealed more than 10^5 colony-forming units (CFU)/mL of *Escherichia coli* sensitive to cephalosporin.

Abdominal ultrasound was significant for normal-sized kidneys, multiple peripelvic cysts, no

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Figure 1 Ultrasound of urinary bladder revealed postvoid urine volume of 400 mL.

hydronephrosis and urinary bladder volume of 424 mL (figure 1). There was no finding of liver disease or portal hypertension.

DIFFERENTIAL DIAGNOSES

1. Posterior reversible encephalopathy syndrome (PRES) associated with severe hypertension.
2. UTI with a urea-hydrolysing organism.
3. Adult-onset urea cycle disorder.

TREATMENT

In the emergency department, a total of 40 mg of intravenous labetalol was administered, followed by 25 mg of oral hydralazine three times a day to control blood pressure, and the patient was discharged on nifedipine XL 90 mg by mouth once daily.

One gram of intravenous ceftriaxone was started empirically for the treatment of UTI, and 30 mL lactulose syrup was given orally and repeated doses were administered targeting 3–4 bowel motions per day.

He received empirical antibiotic treatment for 3 days, which was changed to amoxicillin/clavulanic acid 500 mg/125 mg twice daily, once antibiotic sensitivities were known, for 7 days total duration of treatment.

His serum ammonia level 4 days later had dropped to 28 $\mu\text{mol/L}$ with complete resolution of confusion.

Although, brain MRI was not done to rule out PRES, a parallel correlation between the course of the decreased levels of consciousness and changes in ammonia levels exists, which makes hyperammonaemia a more plausible cause of his impaired level of consciousness.

OUTCOME AND FOLLOW-UP

On the day of admission, blood pressure was controlled after initial treatment. In spite of that, he remained confused without improvement in his mentation.

On the fourth day of admission, his mental status improved remarkably, with a 'Glasgow Coma Scale' of 15, while ammonia level dropped to a normal level following initiation of antibiotics, relieved of the obstruction and lactulose. However, his creatinine and urea levels remained unchanged (figure 2A–C). The patient was subsequently cleared and discharged in a good condition.

DISCUSSION

Hyperammonaemia is a known sequel to decompensated liver disease; however, as noted in our patient, liver function was within normal limits.

In this situation, other differential diagnoses of hyperammonaemia must be exercised.

Other explanations for non-hepatic hyperammonaemia include adverse medication effects, UTI and late-onset enzymatic deficiencies.¹

Non-hepatic hyperammonaemia with or without encephalopathy is not an uncommon clinical finding in elderly patients with UTI.

An observation study conducted by Kenzaka *et al*² estimated the prevalence of this clinical syndrome to be 8.3% of the cohort.

All of these patients demonstrated clinical evidence of urinary tract obstruction and positive urine culture for urease-producing and non-urease-producing organisms.

This finding suggests that urinary tract obstruction may be the main player in the pathogenesis of hyperammonaemia secondary to UTI and the presence of urease-producing organisms is a secondary factor.

Figure 2 (A–C) Plotting the changes in ammonia level, creatinine, blood pressure and Glasgow Coma Scale throughout admission.

Laish *et al*¹ suggested a hypothesis in which interactions between urine pH changes and stasis, in addition to ammonia production by the bacteria, resulted in hyperammonaemia and encephalopathy.

He described the conversion of most of the produced ammonia to charged ammonium in the physiological urine pH (range between 5.5 and 7 with an average of 6.2).

In the presence of UTI, urease enzyme produced by multiplying bacteria will generate two molecules of ammonia (NH₃) per each urea molecule, and in the presence of associated urinary stasis, massive productions of ammonia will consume readily available proton ion (H⁺) and create an alkaline medium.

The alkaline environment will prevent further conversion of ammonia (NH₃) to ammonium ion (NH₄⁺); hence, the concentration of uncharged ammonia will increase dramatically.

Since ammonia is lipid soluble and electrically neutral, it can easily cross the urinary epithelium to urinary bladder venous drainage and systemic circulation bypassing the hepatic circulation.³

This unique acid-base property of ammonia has been used in the treatment and prevention of hepatic encephalopathy in patients with cirrhosis, where the administration of non-absorbable lactulose creates acidic media that enhance conversion of ammonia (NH₃) to ammonium ion (NH₄⁺) and (trapping) ammonia preventing further systemic absorption via the gut mucosa.

Non-hepatic hyperammonaemia secondary to UTI illustrates the classic interaction between the host factors causative agent and environment and might explain why most of the reported cases of infection-induced non-hepatic hyperammonaemia encephalopathy have occurred in children with congenital urinary tract defects, with a background of urinary stasis,⁴ or neuropathic bladder,⁵ which created a favourable media for recurrent infection.

Interestingly enough, some cases of encephalopathy were reported in adults with UTIs and no recognised urinary tract anomalies.^{2 6–10} Frequent pathogens of both urease-producing and non-urease-producing organisms have been implicated in UTI-related hyperammonaemia such as *Proteus mirabilis*, *Klebsiella* species,^{6 8} *E. coli*,¹¹ *Morganella morganii*, corynebacteria^{7 9 10} and diphtheroid.¹² Our patient developed a UTI by *E. coli*, which is commonly not considered a urease producer.

A similar association has been described by Cordano *et al*¹¹ in a 66-year-old woman with a neurogenic bladder who developed hyperammonaemic encephalopathy in two occasions following UTI with *E. coli*. They hypothesised that causative bacteria developed the ability to produce urease, although this could not be confirmed directly by a laboratory test.

Bladder wall inflammation that resulted from infection leads to impairment of barrier function of urothelial cells and

facilitates absorption of ammonia across the inflamed urothelium even when a non-urease-producing organism is implicated, contributing to hyperammonaemia.

Treatment of the UTI and relieving obstruction successfully reduced the blood ammonia level, with complete clinical recovery and improvement of confusion.

Learning points

- ▶ Hyperammonaemia is often caused by decompensated liver disease.
- ▶ Non-hepatic causes can sometimes result in hyperammonaemia severe enough to cause symptoms.
- ▶ 'Anchoring' can bias clinical judgement. It can be avoided by exploring for non-hepatic causes when facing clinical scenarios with symptomatic hyperammonaemia and normal liver function.

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