CASE REPORT

Hyperammonaemic encephalopathy following an uncomplicated surgery

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SUMMARY

A 59-year-old woman who underwent an uncomplicated exploratory laparotomy, adhesiolysis, small bowel resection and anterolateral thigh flap had a complicated postoperative period characterised by wound dehiscence and poor nutritional intake. 29 days postoperatively, a tremor developed in her upper limbs associated with weakness. Her Glasgow Coma Scale (GCS) fell to 4 and she was transferred to the intensive care unit. The patient was reviewed by multiple specialists and multiple differentials were considered and eliminated. Eventually, investigations revealed hyperammonaemic encephalopathy, being a result of low arginine and potentially small intestinal bacterial overgrowth. Following treatment with sodium benzoate, sodium phenylbutyrate and arginine along with haemodialysis and rifaximin, GCS and hyperammonaemia rapidly improved. She was stepped down to surgical high-dependency unit, continued arginine therapy with total parenteral nutrition and percutaneous endoscopic gastrostomy feeds. She was discharged with regular follow-up from surgeons and biochemistry and continues oral arginine therapy.

BACKGROUND

Hyperammonaemia is a potentially life-threatening condition which can manifest in reduced conscious level, neurological signs, cerebral oedema, brain herniation and coma.^{1,2} Ammonia levels may be acutely elevated following gastrointestinal bleeds, infections caused by urease-positive bacteria and total parenteral nutrition (TPN).¹ The liver has a major role in ammonia metabolism involving the urea cycle and impaired liver function either due to urea cycle disorders, liver disease or medications which impair hepatic function can lead to hyperammonaemia.¹ Furthermore, hyperammonaemia can be a result of small intestinal bacterial overgrowth (SIBO) due to increased ammonia production by urease-positive bacteria.³

We describe an interesting case whereby a patient developed hyperammonaemic encephalopathy most likely secondary to low levels of arginine impacting on urea cycle efficiency and SIBO. We hope that from this case, other medical professionals will be more aware of when to investigate for hyperammonaemia and to recognise symptoms and signs, additionally, to begin treatment with advice from biochemistry as soon as possible.

CASE PRESENTATION

We present a 59-year-old woman with a medical history of hypothyroidism, pseudohypoparathyroidism, chronic plaque psoriasis, hypertension and asthma. She has had chronic abdominal wounds since 2006 following a failed repair of an epigastric hernia and chronic malnutrition which was addressed with percutaneous endoscopic gastrostomy (PEG) tube insertion in 2012. She was admitted for exploratory laparotomy, adhesiolysis, small bowel resection, anastomosis and anterolateral thigh flap (ALT) reconstruction of the abdominal wall in September 2016.

Postoperatively, the ALT flap was healthy, 2 units of red blood cells were transfused due to haemoglobin being 7 g/dL and albumin had decreased to 19 g/L from a baseline of 30 g/L. TPN was started by the general surgeons to provide nutritional support.

Twelve days postoperative, TPN administration was stopped following a central line blockage and dieticians reported that the patient was only taking approximately 1200 kcal daily, insufficient to help wound healing. Both the ALT flap and donor site were poor to heal, and required washout and frequent dressings to dehiscent areas. Albumin continued to fall to 14 g/L by day 25 postoperative and PEG feeding was resumed.

On day 33, the patient complained of feeling nauseous and of a new fine tremor in her hands. Neurological examination of the upper and lower limbs was unremarkable and cranial nerves intact.

By day 35, her Glasgow Coma Scale (GCS) was 14 (E4, V4, M6) and she had bilateral twitching of legs and arms with a new weakness of the left arm, scoring 4/5 on the Medical Research Council power scale. She was reviewed by neurology who felt her symptoms were either due to infection, encephalitis or vascular causes and was commenced on intravenous aciclovir. Lumbar puncture excluded a central nervous system infection, and cerebrospinal fluid (CSF) culture did not yield any organisms. A head CT showed no acute changes suggestive of stroke or any vascular abnormality.

GCS fell to 9 (E2, V2, M5) on day 38. She was maintaining her own airway and pupils were reactive to light. Head CT scan was again normal. Blood tests showed a raised white cell count (WCC), neutrophilia and hypomagnesaemia. Magnesium and phosphate were supplemented to prevent development of refeeding syndrome. Levels of magnesium normalised the next day. Intravenous gentamicin and clindamycin were commenced

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following microbiology advice to treat an infection at the ALT flap donor site.

Two days later, she was unconscious, with GCS 4 (E1, V1, M2) and was admitted to intensive care for suspected viral or metabolic encephalopathy. Arterial blood gas (ABG) showed a respiratory alkalosis and respiratory rate was 25 breaths/min. She was intubated and sedated with propofol and alfentanil.

Biochemistry were contacted regarding a metabolic cause of encephalopathy and recommended testing ammonia levels which came back at 295 $\mu\text{mol/L}$ (reference interval $<50 \mu\text{mol/L}$).

Plasma amino acids were also analysed and found to be low in arginine (26 $\mu\text{mol/L}$; reference interval 20–140 $\mu\text{mol/L}$) and glutamine levels were markedly raised (1916 $\mu\text{mol/L}$; reference interval 300–900 $\mu\text{mol/L}$).

Gastroenterology also reviewed the patient and considered SIBO as a potential cause of hyperammonaemia. Although jejunal aspiration or breath test could not be performed, the patient had multiple risk factors for SIBO including malnutrition, fistulae, antibiotic therapy and postoperative ileus. Additionally, fibroscan was normal, excluding a cirrhotic liver disease causing hyperammonaemia.

Intravenous therapy and haemodialysis was commenced to reduce ammonia levels and TPN administered to provide calories. Over 7 days in intensive care, ammonia reduced to 31 $\mu\text{mol/L}$, she was extubated and GCS returned to 15.

Following observation in surgical HDU (High Dependency Unit), the patient was brought down to the surgical ward, oral feeding encouraged and was discharged with oral arginine 8g daily, which she is still taking regularly.

INVESTIGATIONS

Admission bloods showed mean corpuscular volume (MCV) 8.1^{14}L (reference interval $8.2\text{--}9.9^{14}\text{L}$), HCO_3 35 mmol/L (reference interval 22–29 mmol/L), glomerular filtration rate 54 mL/min/1.73 m^2 , albumin 30 g/L (reference interval 35–50 g/L), Mg 0.67 mmol/L (reference interval 0.7–1.0 mmol/L) and mildly elevated liver function tests. Postoperatively, the patient had a low haemoglobin at 9.5 g/dL (reference interval 12–16 g/dL), MCV 8.1^{14}L , white cell count (WCC) $13 \times 10^9/\text{L}$ (reference interval $4\text{--}10 \times 10^9/\text{L}$), neutrophils $11.4 \times 10^9/\text{L}$ (reference interval $1.5\text{--}7 \times 10^9/\text{L}$), albumin 19 g/L.

On days 35 and 38, a head CT scan was performed to exclude stroke in light of the neurological symptoms and showed no acute changes.

To exclude meningitis and encephalitis, a lumbar puncture was performed. The results of which were all normal and CSF culture did not yield any organisms.

Bloods taken showed PO_4 1.16 mmol/L (reference interval 0.8–1.5 mmol/L), albumin 15 g/L, potassium 4 mmol/L (reference interval 3.5–5.3 mmol/L), WCC $14.4 \times 10^9/\text{L}$, neutrophils 10.8 (reference interval $1.5\text{--}7 \times 10^9/\text{L}$), Mg 0.61 (reference interval 0.7–1 mmol/L).

On admission to the intensive care unit (ICU), ABG showed a respiratory alkalosis: pH 7.520, PCO_2 3.74 kPa, PaO_2 12.96 kPa, base excess 0.1, HCO_3 24.5 mmol/L. When this interpretation was put in context with hyperammonaemia the next day, it was clear that the raised ammonia was contributing to the increased respiratory drive.

After biochemistry advice, plasma amino acids and ammonia levels were analysed and revealed a strikingly elevated glutamine of 1916 $\mu\text{mol/L}$ and arginine being on the low side of normal at 26 $\mu\text{mol/L}$. Ammonia levels were measured to be 295 $\mu\text{mol/L}$. These levels required immediate action and led

to the commencement of sodium benzoate, sodium phenylbutyrate and arginine therapy along with haemodialysis and rifaximin.

An electroencephalogram performed showed flat featureless episodes and slow wave activity which was consistent with hyperammonaemia. Also, fibroscan was negative for cirrhotic liver disease, making the cause of hyperammonaemia unlikely to be hepatic in origin.

DIFFERENTIAL DIAGNOSIS

An acute presentation of neurological symptoms in the upper limbs and later leading to a reduced conscious level raises the possibility of whether an anterior circulation stroke has occurred. To exclude this diagnosis, a head CT was performed which showed no acute changes. Additionally, no space occupying lesions were identified. Meningitis and encephalitis were other important differentials to exclude and were discounted following lumbar puncture analysis and culture. Furthermore, intravenous aciclovir was started to cover viral encephalitis while awaiting culture results which came back negative. Refeeding syndrome was also considered to be a potential cause of the patient's symptoms and magnesium and phosphate supplements started; however, potassium and phosphate levels were not in keeping with this diagnosis and following discussion with biochemistry, this diagnosis was thought to be unlikely due to the strict monitoring of feeding and gradual increase in TPN and PEG feeding organised by the dieticians and biochemistry team.

A metabolic encephalopathy was postulated and investigated by measuring plasma ammonia and was found to be very high at 295 $\mu\text{mol/L}$. Glutamine levels were also high and arginine on the low side. This prompted the immediate treatment following advice from clinical biochemistry.

To determine the cause of hyperammonaemia, a fibroscan was performed, excluding cirrhosis. There was no evidence of acute gastrointestinal bleeding and inheritable urea cycle disorders were excluded. Gastroenterology believed the cause to be due to small intestinal bacterial overgrowth. Although jejunal aspiration or breath test could not be performed, the patient had several risk factors for the development of this including being malnourished, having fistulae, undergoing abdominal surgery which increased ileus risk and being treated with multiple antibiotics. We believe the hyperammonaemia to be due to a combination of SIBO with low arginine which limited the activity of the urea cycle.

TREATMENT

In the management of hyperammonaemia, a loading dose of sodium benzoate 5.5 g/ m^2 , sodium phenylbutyrate 5.5 g/ m^2 and arginine 4 g/ m^2 was mixed in 500 mL 5% dextrose/ m^2 and given intravenously over 90 min. A maintenance infusion was then given over 24 hours and repeated until ammonia levels normalised.

In conjunction with the infusion, the patient underwent haemodialysis. Rifaximin 550 mg was also given twice daily to reduce intestinal ammonia absorption.

Total parenteral nutrition and PEG feeding were used to provide calories during recovery.

Clindamycin 600 mg three times daily was also given for wound infection around the ALT site and donor site. Intravenous gentamicin was later commenced to provide broad Gram-negative cover.

The patient continues on oral arginine 8g daily.

OUTCOME AND FOLLOW-UP

Ammonia levels normalised and GCS returned to normal with no neurological impairment following several days in ICU. The cause of hyperammonaemia in this case was believed to be multifactorial, with SIBO being an important contributor along with having low levels of arginine which would impact on activity of the urea cycle.

The patient is undergoing regular follow-up with general and plastic surgeons as well as biochemistry while continuing oral arginine treatment.

DISCUSSION

We have presented a case of hyperammonaemic encephalopathy of which the cause was multifactorial. After ruling out pre-existing liver disease and inherited urea cycle disorders, we believe that SIBO was a contributing factor. This patient had multiple risk factors for the condition including recent abdominal surgery carrying the risk of ileus, she was chronically malnourished, had multiple enterocutaneous fistulae and had received multiple courses of antibiotics during her postoperative stay, all of which have been documented as potential risk factors.⁴ Furthermore, the addition of rifaximin to the patient's treatment would have reduced the intestinal absorption of ammonia, improving her condition.

The ammonia produced from SIBO would have been transported to the liver for metabolism, however, with the patient having low levels of arginine, efficiency of the urea cycle would have been diminished, leading to accumulation of ammonia within the systemic blood stream. Ammonia is able to cross the blood–brain barrier and is detoxified by astrocytes, leading to accumulation of glutamine. Glutamine levels in our patient were measured at 1916 $\mu\text{mol/L}$, significantly higher than normal ranges. The raised glutamine levels result in cerebral oedema and contribute to the neurological deficits seen in our patient.^{5,6} It is also plausible that a portosystemic shunt existed in our patient and allowed ammonia to bypass the liver metabolism, leading to encephalopathy.

We have identified several case reports of non-hepatic hyperammonaemia leading to encephalopathy including acute gastrointestinal haemorrhage, slow transit constipation and a thrombus obstructing the portal vein in combination with a shunt from the mesenteric veins and the inferior vena cava, bypassing portal circulation.^{7,8} SIBO is often associated with cirrhosis and is linked to encephalopathy via excess gut ammonia production.³ However, in our case, there was no pre-existing liver disease and no evidence of cirrhosis.

A report describes the potential of uncontrolled refeeding which led to hyperammonaemia, hypophosphataemia and encephalopathy. The authors believed hyperammonaemia to be due to an overload of nitrogen from feeding and impaired urea cycle function.⁹ However, blood results did not fit with this clinical picture in our patient and refeeding in our patient was tightly controlled, being guided by dietitians and clinical biochemistry.

To the best of our knowledge, this is the first reported case of a patient who developed hyperammonaemic encephalopathy secondary to low arginine levels and potentially SIBO and provides several learning points.

Learning points

- ▶ Hyperammonaemia can present early with neurological symptoms and signs.
- ▶ Respiratory alkalosis is associated with hyperammonaemic encephalopathy.
- ▶ Seek specialist advice regarding management of hyperammonaemia and initiate treatment immediately.
- ▶ The immediate treatment of hyperammonaemia involves a loading dose of sodium benzoate 5.5 g/m², sodium phenylbutyrate 5.5 g/m² and arginine 4 g/m² which is mixed in 500 mL 5% dextrose/m² and given intravenously over 90 min. A maintenance infusion is then given over 24 hours and repeated until ammonia levels normalise. Haemodialysis can also be considered in addition to the aforementioned treatment.
- ▶ Try to identify underlying cause of hyperammonaemia.

Contributors SM: involved with requesting of patient notes, interpretation of medical notes, collection of blood results. Writing of report and revising drafts of report. KM: involvement in planning of report, collection of data from medical records, interpretation of blood results and notes on postoperative care. Also involved in writing of report and revising drafts for finalisation. KD: chiefly involved in the gathering of biochemical data for patient and providing information on the treatment of the patient; involved in writing of treatment section and reviewing report for finalisation. SS: involved in the collection of patient blood results, interpretation of results and literature searching; reviewed and approved final draft.

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