CASE REPORT

Coma query cause

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Accepted 10 April 2015

SUMMARY

A 54-year-old woman with coeliac disease was admitted to hospital electively for supplemental nutrition. Shortly after feeding started she deteriorated into a hyperammonemic coma with refeeding syndrome, requiring an extensive intensive care admission. Urea cycle disorders were investigated and a biochemical diagnosis of ornithine transcarbamylase deficiency was made. This is a rare diagnosis in the adult population. This case report summarises protein metabolism, urea cycle disorders and the challenges of management.

BACKGROUND

Protein is an essential dietary component, as proven by animal studies in the early 19th century showing that those being fed only fats and carbohydrates lost a large amount of body weight and had severe wasting of muscles and other tissues.¹ The average daily protein requirement is 0.6 g/kg, with approximately 12% being excreted in faeces. The remainder is hydrolysed to free amino acids prior to absorption. Approximately half of the common amino acids are categorised as being 'essential', as their biosynthesis does not occur in man. The fate of absorbed amino acids reflects metabolic demand. Free amino acids can be deaminated and the ketoacid products oxidised to release energy or provide precursors for gluconeogenesis. Amino acids are also used to synthesise body proteins, including structural proteins, enzymes, plasma proteins and hormones. Residual nitrogenous waste is excreted as urea. These processes are all part of a dynamic equilibrium with continuous breakdown and replacement of proteins and amino acids. The direct deamination of certain amino acids results in the formation of ammonium ions, which are highly toxic. The normal plasma concentration is <50 µmol/L, with levels above 80 µmol/L causing altered consciousness, convulsions, coma and even death. Ammonia is normally safely transported to the liver as glutamine, which is deaminated to generate glutamate and subsequently converted to aspartate for entry to the urea cycle. Alanine can also be employed. Generation of glutamine in peripheral tissues can deplete levels of mitochondrial α-ketoglutarate, and impair the Krebs cycle and energy production. Failure of the urea cycle leads to disturbance of glutamate and glutamine levels. Glutamate is a neurotransmitter and a substrate for the production of another neurotransmitter, γ amino butyric acid.

Within the liver, ammonia and aspartate are the substrates for the synthesis of urea. Urea cycle disorders result from a deficiency in one of six enzymes—carbamoylphosphate synthetase I,

argininosuccinate synthase, argininosuccinate lyase, arginase, ornithine transcarbamylase (OTC) and N-acetylglutamate synthase.² N-acetylglutamate synthase is not a true urea cycle enzyme, but acts as a gatekeeper and is responsible for the activation of the first enzyme of the cycle.

OTC deficiency, an X linked condition, is the most common urea cycle disorder. OTC deficiency was first reported in females in 1962 and 10 years later in males.^{3–4} It is now recognised that only 15% of female carriers ever show symptoms. Affected males rarely survive past the first week of life. Typical presentation is 24–48 h after birth when feeding starts with features such as somnolence, hypothermia, vomiting and seizures.⁵ Cerebral oedema causes hyperventilation and consequent respiratory alkalosis. Progression of encephalopathy eventually leads to hypoventilation, respiratory depression and death.⁶

Less frequently, urea cycle disorders can present in adulthood, the most common forms being OTC deficiency and partial enzyme deficiencies. Symptoms are often more subtle, with chronic vomiting, seizure disorders and psychiatric illness. They usually manifest following increased protein intake and during periods of catabolic stress.⁷ Diagnosis is initially suspected when serum ammonia levels exceed 80 µmol/L in conjunction with normal blood glucose and a normal anion gap. More specific laboratory tests are required to confirm diagnosis including quantitative plasma and urine amino acid analysis to determine which enzyme is deficient. OTC deficiency shows absent or very low citrulline and arginine serum levels with raised glutamine and orotic acid serum levels. Molecular testing is approximately 80% accurate, but tissue confirmation can be achieved with a liver biopsy. The mitochondrial enzyme OTC degrades rapidly after death, so biopsy needs to be taken prior or immediately after death. DNA mutation analysis can also be used with >340 mutations of single base substitutions reported.⁸

Urea cycle disorders are typically a disease of the newborn, with an incidence of 1:30 000 live births. With the exception of OTC deficiency, which is X linked, the disorders demonstrate an autosomal recessive inheritance pattern.

Altered consciousness is a common presenting symptom in the emergency department and on the wards throughout hospitals, with a vast differential diagnosis. This case report highlights a rare cause of coma in adults that is not commonly considered.

CASE PRESENTATION

We present a case of OTC deficiency in a 54-year-old woman with coeliac disease, who was admitted to hospital electively for supplemental nutrition.

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To cite: Wood GE, McNicholas J. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-205592

The patient's medical history included a number of unrelated conditions: renal calculi, lichen planus, iron deficiency anaemia and osteoporosis. One year prior to this presentation, a diagnosis of coeliac disease had been established by duodenal biopsy, capsule endoscopy and detection of autoantibodies against tissue transglutaminase (TTG).

Admission to hospital was precipitated by a significant weight loss of 12.7 kg over a period of 6 months, following bereavement. Although she had adhered to a gluten free diet with some symptomatic relief, there was worsening cachexia, and this was felt to represent a combination of malabsorption due to coeliac disease and demotivation with depressed mood. Throughout that year, her TTG antibodies had been persistently raised with mildly deranged liver function tests. After careful supplemental nutrition, there was initial evidence of good progress.

However, during week 3 of her admission, she was urgently referred for intensive care with altered consciousness, with an initial Glasgow Coma Scale (GCS) score of 3. She was intubated and ventilated, and transferred to the intensive care unit (ICU) for further assessment. An urgent X-ray CT of the head showed no focal lesion, infarct or haemorrhage, but there were subtle changes within the brainstem, which may have represented simple artefact (figure 1).

A radiological diagnosis of central pontine myelinolysis was considered, however, hyponatraemia was not present. The patient's electrolyte profile reflected refeeding syndrome (with an elevated serum ammonia of 437 $\mu\text{mol/L}$; normal range 0–50 $\mu\text{mol/L}$). Enteral feeding was immediately stopped, and lactulose and rifaximin were started to help reduce the ammonia level. An EEG showed symmetrical diffusely slow activity, which was consistent with a severe encephalopathic process. Electrolytes magnesium, potassium and phosphate were also carefully replaced, to allow controlled correction of the derangements. A CT of the chest, abdomen and pelvis was performed, and was unremarkable, with the exception of a small amount of ascites. There was no portal vein thrombosis and no evidence of small bowel lymphoma.

After discussion with King's College London Liver Unit, the differential diagnosis was felt to include refeeding syndrome, hepatic dysfunction or abnormal metabolism of ammonia. A diagnosis of a urea cycle disorder was specifically investigated and on day 2 of ICU admission, a biochemical diagnosis of OTC deficiency was made on the basis of elevated serum orotic acid and glutamine levels, as well as normal citrulline and arginine. The British Inherited Metabolic Disease Group guideline was followed for emergency amino acid replacement. Guidance for feeding and management was sought from University

College London's Adult Inherited Metabolic Diseases Unit and the department of Metabolic Medicine at Southampton General Hospital.

Concurrently, methicillin-sensitive *Staphylococcus aureus* (MSSA) was cultured from the patient's serum samples sent from the central venous catheter (CVC), at time of insertion. Management entailed the broad-spectrum antibiotic meropenem and a transthoracic echocardiogram in order to investigate the possibility of one of the most common sources of infection, bacterial endocarditis. However, a source could not be identified.

Forty-eight hours after the reintroduction of a low protein, high sugar, gluten free oral diet, the patient developed an ileus, with a CT scan showing a grossly dilated small bowel compressing the large bowel at the splenic flexure and causing mechanical obstruction. Total parenteral nutrition was given and the obstruction was resolved by flatus tube decompression. After a further 10-day admission in the ICU, the patient was discharged to the gastroenterology ward with a formal nutrition plan and continuing oral amino acid replacements.

Unfortunately, the patient suffered a further deterioration, leading to readmission to the ICU with a GCS of 3, and in type II respiratory failure (pCO_2 9.4 kPa). This was thought to be secondary to diaphragmatic splinting as a consequence of her tense distended abdomen. Her serum ammonia levels had also risen from 41 to 96 $\mu\text{mol/L}$ in 24 h. She was intubated and ventilated and transferred to ICU with a vasopressor requirement. Nine litres of ascitic fluid were drained (transudate with a low white cell count). The ascitic fluid did have a high serum ascites albumin gradient, usually indicative of portal hypertension, however, review of the abdominal CT scan confirmed patent portal and hepatic veins.

During this readmission to the ICU, the patient failed two attempts at weaning off ventilation: she improved quickly when her respiratory system was supported, but deteriorated rapidly when separated from the ventilator. This process was complicated by a further pseudo-obstruction, relative acute kidney injury (creatinine 93 $\mu\text{mol/L}$), worsening thrombocytopenia and increasing norepinephrine, dobutamine and hydrocortisone need. Blood cultures grew *Klebsiella* with a repeat ascitic tap confirming spontaneous bacterial peritonitis while a further 16 L of ascites was drained with platelet infusion cover (in view of her very low platelet count and consequent risk of bleeding). Despite treatment with meropenem and fluconazole, the patient continued to decline and developed a hospital-acquired pneumonia. As she was tolerating the endotracheal tube without sedation it was possible to discuss prognosis with the patient along with her family; consequently, she was extubated and an end-of-life care plan instigated.

OUTCOME AND FOLLOW-UP

Hospital postmortem confirmed bronchopneumonia as the cause of death, precipitated by severe malnutrition as a consequence of OTC deficiency. Corneas were taken as tissue donation. There was no suitable serum or tissue sample for genetic testing. Family members have been referred for genetic testing and counselling.

DISCUSSION

The incidence of OTC deficiency is approximately 1 in 70 000.⁹ In some affected individuals, the clinical signs are less severe and present in the fifth or sixth decade of life. These patients are typically heterozygous females, with the subtlety of the initial symptoms meaning that adult-onset OTC deficiency is commonly missed on first presentation. Consequently, a delay in

Figure 1 CT of the head showing a slightly bulky pons and low attenuation of the middle cerebellar peduncles.

recognition leads to late instigation of treatment, a fact that is reflected by the extremely high mortality. Since the differential diagnosis for unexplained coma is extensive, and the clinical manifestations of urea cycle disorders are non-specific, there needs to be a high index of suspicion to ensure a correct diagnosis is ascertained. Plasma ammonia levels should therefore be measured in routine tests in all patients.

Quantitative plasma amino acid analysis is necessary for the initial diagnosis of urea cycle disorders with early involvement of liver and metabolic specialists being essential to expedite diagnosis. Previously, the diagnostic gold standard had been enzyme analysis by liver biopsy. This is, however, currently restricted to those cases where OTC deficiency is not confirmed by the presence of a known pathogenic mutation.

The difficulty of protein balance was key in this case. The patient was in a catabolic state, initially from malnutrition and psychological stress, but exacerbated by concurrent sepsis with MSSA bacteraemia, spontaneous bacterial peritonitis and pneumonia. These factors, in combination, significantly increased her metabolic stress and hence her protein need. However, the introduction of protein via feeding caused toxic ammonia levels to rise, resulting in a cycle of clinical improvement and deterioration, complicated by liver dysfunction and ascites. She suffered severe muscle wasting and as a result was not able to separate successfully from the ventilator.

The patient's liver function tests were noted to be deranged 6 months prior to admission and this had been initially attributed to coeliac disease. There is emerging clinical evidence that urea cycle disorders may be complicated by hepatic dysfunction,¹⁰ arousing suspicion of chronic OTC deficiency, with delayed presentation, as in this case. Hospital postmortem for this patient revealed a fine granular micronodular liver in keeping with cirrhosis. It has been observed that serum ammonia levels as high as 140 $\mu\text{mol/L}$ can otherwise be tolerated and asymptomatic in chronic hyperammonemia.¹¹

This patient had a clear trigger, having started nasogastric (NG) feeding shortly before losing consciousness, with the increased protein intake revealing her enzyme deficiency. Clearance of serum ammonia was achieved quickly by stopping the NG feed and initiating emergency intravenous therapy with expert guidance. This included enzyme catabolytes L-citrulline and L-arginine, and 'ammonia scavengers' in the form of sodium phenylbutyrate and sodium benzoate. Rapid reduction of serum ammonia levels is imperative to reduce morbidity and mortality. Renal replacement therapy (RRT) is indicated if serum ammonia levels continue to rise despite medical treatment or if levels are persistently $>350 \mu\text{mol/L}$. Continuous venovenous haemodiafiltration has been noted to be the preferred method of RRT, achieving more rapid clearance of ammonia.¹²

Heterozygous females have a 50% chance of transmitting the disease causing mutation with each pregnancy, and males who inherit the mutation are symptomatic, although 33% of cases

are due to de novo mutations. Our patient had one son, who was not affected but has been referred for genetic counselling.

Learning points

- ▶ Late-onset ornithine transcarbamylase deficiency should be considered in any adult with a history of recurrent vomiting, migraine headaches, reye-like syndrome, encephalopathic or psychotic episodes, seizures and/or unexplained 'cerebral palsy'.¹³
- ▶ The key initial investigation is serum ammonia, and consideration of the diagnosis early if the ammonia is elevated.
- ▶ All cases should be managed in close consultation with experts in metabolic disease. It is a potentially fatal yet treatable cause of coma.
- ▶ For a definitive diagnosis it is important to perform plasma or tissue genetic testing.

Contributors GEW wrote the case report. JM was the supervisor.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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