CASE REPORTS

Non-hepatic hyperammonaemia: an important, potentially reversible cause of encephalopathy

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Abstract

The clinical syndrome of encephalopathy is most often encountered in the context of decompensated liver disease and the diagnosis is usually clear cut. Non-hepatic causes of encephalopathy are rarer and tend to present to a wide range of medical specialties with variable and episodic symptoms. Delay can result in the development of potentially life threatening complications, such as seizures and coma.

Early recognition is vital. A history of similar episodes or clinical risk factors and early assessment of blood ammonia levels help establish the diagnosis. In addition to adequate supportive care, investigation of the underlying cause of the hyperammonaemia is essential and its reversal, where possible, will often result in complete recovery. Detection of an unborn error of metabolism should lead to the initiation of appropriate maintenance therapy and genetic counselling.

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Hyperammonaemia is a recognised cause of encephalopathy characterised by episodic confusion and coma. Hepatic hyperammonaemia is usually seen in the setting of decompensated liver disease when the diagnosis is reasonably straightforward because of accompanying signs of chronic liver disease. However, there are a number of non-hepatic causes of hyperammonaemia severe enough to cause confusion and coma. These cases are rare, have diverse aetiologies, and as a result tend to present to many different specialties. In addition, they may lack accompanying clinical signs, so the doctor is presented with a confused or unconscious patient of unknown cause. Unless there is a high index of suspicion the diagnosis may easily be missed and the potential for reversibility and cure lost.

Here we review non-hepatic hyperammonaemia and describe three cases that illustrate important aspects of its pathophysiology and clinical management. In particular, these cases highlight the diverse nature of the condition and the importance of establishing a diagnosis and treatment strategy, borne out by the fact that all had a favourable outcome.

Case reports

CASE 1

A 20 year old man was admitted to a local hospital with two days of inappropriate behaviour, clumsiness, drowsiness, memory loss, slurred speech, and abdominal discomfort. Since the age of 2 years he had suffered recurrent rectal bleeding and investigation had revealed haemorrhoids. Bleeding from his rectum had continued over the years but had been worse recently.

On examination he was confused. His Glasgow coma scale score (GCS) was 15/15. Neurological and general examination was normal, with no stigmata of chronic liver disease.

Investigations showed a leucocytosis (leucocyte count $22 \times 10^9/l$) and serum bilirubin level of $32 \mu\text{mol/l}$. Other liver function tests, haemoglobin, platelet count, serum electrolytes, glucose, clotting profile, arterial blood gas analysis, and toxicology screen were normal. Cerebrospinal fluid examination (CSF) and computed tomography of the brain were normal.

Shortly after lumbar puncture his conscious level decreased (GCS 4/15). Plantar reflexes became extensor and he developed tonic-clonic seizures. At this point he passed melaena stool.

After transfer to our hospital his GCS score was 6/15. The pupils were dilated but reactive to light. Plantar reflexes remained extensor with no other focal neurological deficit. Upper gastrointestinal endoscopy was normal. Venous blood ammonia was raised at $450 \mu\text{mol/l}$ (normal $<80 \mu\text{mol/l}$). A diagnosis of hyperammonaemic encephalopathy was made.

Because of continued heavy gastrointestinal bleeding his encephalopathy worsened. He required ventilatory support and his intracranial pressure was found to be raised. A mesenteric angiogram demonstrated unusual portal vasculature with a large inferior mesenteric vein forming a direct mesocaval shunt with the rectal veins and the systemic circulation (fig 1); the portal vein was absent. His inferior mesenteric vein pressure was raised at 16 mm Hg. There was no evidence of hepatocellular failure and a liver biopsy was normal. In view of continued gastrointestinal bleeding and raised intracranial pressure emergency surgery was performed and a superior mesocaval shunt formed reducing inferior mesenteric vein pressure to 5 mm Hg. This stopped the gastrointestinal bleeding. He gradually regained consciousness and ammonia levels returned to normal. He was discharged home and remains well.

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Figure 1 The early phase of the mesenteric angiogram (A) shows dense contrast filling the splenic artery (SA) and a normal sized spleen. Exiting the spleen contrast flows via the splenic vein (SV) into a grossly enlarged inferior mesenteric vein (IMV). The portal vein is not seen and there is no evidence of cavernous transformation of the portal vein or collateral vessels. The filling of the inferior vena cava (IVC) on the later phase of the angiogram (B) confirms that the IMV forms a lower mesorectal shunt with the rectal veins and systemic circulation.

Hyperammonaemia was thought to be due to the massive gastrointestinal bleed resulting in absorption of excess nitrogen—the ammonia generated bypassing the liver through a distal portosystemic shunt, allowing a significant rise in systemic blood ammonia levels. Although a liver biopsy was normal, the size of the nitrogen load and extent of shunting was sufficient to cause encephalopathy. The fact that the blood ammonia level fell and the patient recovered once the bleeding stopped supports this theory. The development of encephalopathy during a gastrointestinal bleed would be an unusual complication of portal vein thrombosis—the cavernous transformation and formation of collateral vessels tend to maintain blood flow to the normal liver, preventing its occurrence. At surgery, the portal hypertensive changes were confined to the distal gastrointestinal tract with varices evident in the ileum, colon and rectum, supporting the fact that this was not a simple portal vein thrombosis. No upper gastrointestinal varices or splenomegaly were seen, suggesting that the huge anomalous inferior mesenteric vein had effectively decompressed the proximal superior mesenteric vein and splenic veins preventing proximal hypertensive problems.

CASE 2

A 55 year old man was admitted to our hospital with two days of progressive lethargy and confusion. For the previous three weeks he had taken codeine phosphate for back pain and had developed constipation. At 6 years of age he had undergone ureterosigmoidostomy for epispadias and bladder extrophy. Subsequently he suffered intermittent bouts of confusion, altered personality, and lethargy. Investigations had found no cause.

On examination he had a GCS of 4/15 and a left sided hemiparesis. He was afebrile, and general examination was normal apart from his abdominal scar and epispadias.

Full blood count, serum electrolytes, glucose, liver function, chest radiography, abdominal ultrasound, and computed tomography of the brain were normal. Arterial blood gases showed mild hypoxia. CSF examination was normal, except there was a CSF protein concentration of 1.67 g/l (normal <0.45 g/l). An electroencephalogram (EEG) showed diffuse non-specific abnormality. Cranial magnetic resonance imaging (MRI) revealed diffuse signal changes throughout the cerebral white matter consistent with cerebral oedema.

Over the next few days his conscious level fluctuated. He developed left sided neglect with conjugate deviation of the eyes to the right and had several generalised tonic-clonic seizures, treated successfully with intravenous phenytoin. His blood ammonia levels were 245 $\mu\text{mol/l}$. Urinary orotic acid and serum amino acid levels were normal.

Hyperammonaemia was thought to be due to slow transit constipation allowing increased absorption of ammonia into the mesenteric blood supply, sufficient to overwhelm hepatic excretory pathways. Despite lactulose and broad spectrum antibiotics he continued to deteriorate and required ventilation. Blood ammonia levels rose to 400 $\mu\text{mol/l}$. Two days later his ureterosigmoidostomy was converted to an ileal conduit. He gradually improved, ammonia levels returned to normal, and he has remained well. A repeat cranial MRI scan was normal.

CASE 3

A 10 year old boy was admitted to a local hospital with a two day history of headache associated with vomiting, agitation, confusion, and slurred speech. After a normal delivery and neonatal period, he subsequently suffered a sixth nerve palsy (Duane's syndrome) and a febrile seizure during infancy. Aged 3 years he had an unexplained episode of vomiting and lethargy lasting six days; this resolved spontaneously. At the age of 6 he was admitted to hospital with an

episode of headache, vomiting, confusion, and drowsiness associated with mild hyponatraemia and non-specific, excess slow wave activity on his EEG. He had been treated with acyclovir for suspected herpes simplex encephalitis and after a quick recovery was discharged.

On examination he was afebrile with a GCS of 15/15. He was disorientated in time and place, but not in person. He was slightly confused with slurred speech. Neurological examination revealed the longstanding sixth nerve palsy, increased tone in the lower limbs with hyper-reflexia and bilateral extensor plantar responses. General examination was otherwise normal.

Full blood count, urea and electrolytes, serum glucose, and clotting screen were normal. Arterial blood gases showed a pH of 7.40 and serum bicarbonate level of 15.6 mmol/l (normal 22–27). Serum alkaline phosphatase was 307 IU/l (normal 30–115) but liver function was otherwise normal. CSF examination and computed tomography head were normal. Electroencephalography showed non-specific changes identical to those of his previous admission. Urinalysis registered “+++” ketones. Serum ammonium and lactate levels were raised at 156 $\mu\text{mol/l}$ and 2.3 mmol/l (normal 0.8–1.2) respectively.

Initial treatment with acyclovir, cefotaxime, and dexamethasone did not result in clinical improvement. He was transferred to our hospital and started on a 10% glucose infusion (6 mg/kg/min), to render him anabolic. Dietary protein was excluded.

A metabolic screen showed raised glutamine levels in serum and CSF, 1345 $\mu\text{mol/l}$ and 2103

$\mu\text{mol/l}$, respectively (normal <750 for both), serum ornithine level 15 $\mu\text{mol/l}$ (normal >25), and a large urinary orotic acid peak.

A diagnosis of late onset ornithine transcarbamylase deficiency was made. After a peak of 170 $\mu\text{mol/l}$ venous blood ammonia returned to normal. He improved without requiring sodium benzoate treatment. Dietary protein was gradually increased without a significant rise in ammonia levels and he was discharged home. Allopurinol loading tests and genetic analysis confirmed both brothers and his mother carried the same affected allele in exon 2 of the ornithine transcarbamylase gene (located on the X chromosome). His family received counselling and advice on emergency management. He has remained well but one sibling has required hospital admission.

In this case the precipitating event was not clear. This is not unusual in urea cycle enzyme deficiencies, though an increased dietary nitrogen load or intercurrent infection may precede clinical deterioration. A gradual onset of symptoms is common to these disorders—a more abrupt presentation should lead to consideration of other causes of raised intracranial pressure.

Discussion

Amino acids, the products of endogenous and exogenous protein digestion, are degraded by hepatic transamination and oxidative deamination to produce ammonia, which is then converted to urea and excreted by the kidneys. Any disruption to this cycle of nitrogen excretion (fig 2) has the potential to cause

Figure 2 Schematic representation of the major sources of ammonia production and its excretory pathway (GI = gastrointestinal, IMV = inferior mesenteric vein).

Table 1 Causes of non-hepatic hyperammonaemia

<ul style="list-style-type: none"> • Inherited defects of the urea cycle enzymes • Transport defects of intermediates in the urea cycle • Organic acidurias • Other metabolic causes <ul style="list-style-type: none"> Hyperinsulinaemic hypoglycaemia Distal renal tubular acidosis Primary carnitine deficiency Fatty acid oxidation defects • Drugs <ul style="list-style-type: none"> Chemotherapy—for example, 5-fluorouracil, asparaginase Sodium valproate Anaesthetic agents—for example, halothane, enflurane • Reye's syndrome* 	<ul style="list-style-type: none"> • Portosystemic shunts† • Urinary <ul style="list-style-type: none"> Urinary diversion—for example, ureterosigmoidostomy and ileal conduit Urinary tract infections Subureteric injection for vesicoureteric reflux • Haematological <ul style="list-style-type: none"> Following allogenic peripheral blood progenitor cell transplantation Multiple myeloma Acute myeloblastic leukaemia, chronic myelocytic leukaemia • Other <ul style="list-style-type: none"> Parenteral nutrition Muscular origin Idiopathic
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*Need to exclude inborn errors of metabolism as possible cause—for example, medium chain acyl-CoA deficiency.

†With normal liver function, as distinct from portosystemic shunts occurring in the context of chronic liver disease where resultant hyperammonaemia may be termed hepatic hyperammonaemia.

hyperammonaemia and the clinical syndrome of encephalopathy.

Firstly, the cycle may not be able to handle a normal nitrogen load (for example, specific enzyme defect or liver cell failure resulting in poor hepatic function); secondly, though liver function is normal, excess nitrogen (for example, from a gastrointestinal bleed or urinary diversion) may oversaturate the liver's excretory capacity; or thirdly, the nitrogen load may bypass the liver, entering directly into the systemic circulation via a portosystemic shunt. Encephalopathy is most commonly seen in patients with liver cirrhosis where the problem is due to a combination of decreased capacity due to liver cell damage and portosystemic shunting of the increased nitrogen load.^{1 2} While hyperammonaemia is present in the majority of patients with hepatic encephalopathy,³ this is not always the case and the underlying neuropathophysiology remains the subject of further research and debate.^{2 4-6} The production of false transmitters, activation of central (γ -aminobutyric acid-benzodiazepine receptors by endogenous ligands, altered cerebral metabolism, disturbed activity of the Na⁺/K⁺ ATPase, and zinc deficiency with deposition of manganese in the basal ganglia have all been proposed as possible contributory factors in the development of encephalopathy in cirrhotic patients.²

Non-hepatic causes of hyperammonaemia may present with an identical clinical syndrome (table 1). Though rare, the underlying cause may be reversible, and potentially curable, or specific therapy in addition to the general measures to reduce hyperammonaemia may be indicated—therefore prompt recognition may be lifesaving.

The first case had a very unusual vascular anomaly which behaved differently to classic portal vein thrombosis, both radiologically and clinically. No flow through the portal vein was seen on mesenteric angiography, the contrast instead passing through a greatly enlarged inferior mesenteric vein to form a large lower mesorectal shunt with the rectal veins and systemic circulation—therefore despite normal liver function, the significant protein load absorbed into the mesenteric blood supply after gastrointestinal haemorrhage, was shunted directly into the systemic circulation, via the inferior vena cava, resulting in hyperammonaemia. It is a matter for speculation as to

the cause of this vascular abnormality. The most common cause of an absent portal vein is portal vein thrombosis at birth, secondary to infection.⁷ Usually, if recanalisation has not occurred, this results in the formation of collateral vessels in the region of the portal vein which were not present in this case. Congenital absence of the portal vein⁸ or congenital pancreatitis may also account for some of the radiological findings. The formation of such a large inferior mesenteric vein may favour a primary vascular malformation, although the presence of other congenital anomalies might be expected if this were the case.⁸ This situation is distinct from the extrahepatic shunting that occurs, usually via multiple collateral vessels, in chronic liver disease associated with portal hypertension, or from iatrogenic portosystemic shunts, though hyperammonaemia results from the same mechanism of hepatic bypass.

Hyperammonaemia arising as a metabolic complication of surgery to create a urinary diversion is well recognised.⁹⁻¹¹ The longer segment of bowel exposed to urine may explain why this arises more commonly after ureterosigmoidostomy than ileal conduits.¹² Ammonia is formed in the colonic lumen, through the bacterial degradation of the large quantities of nitrogenous compounds excreted in the urine. Production is enhanced by the presence of urease-producing, Gram negative bacilli.^{13 14} As the diversion retains its venous drainage, ammonia crosses the colonic wall and is absorbed into the portal circulation. In the majority of patients, with normal liver function, excess ammonia is excreted by hepatic metabolism—via the urea cycle (fig 3). However, hyperammonaemia sufficient to result in encephalopathy may still occur even in the setting of a patient with normal liver function.¹⁵ Increased production of ammonia, sufficient to over-saturate hepatic excretory pathways—for example, after the action of urea-splitting bacteria or delayed colonic transit; direct diffusion of ammonia into the inferior vena cava bypassing the liver (via the haemorrhoidal veins after urinary diversion or internal iliac veins in the case of a neurogenic bladder); and decreased metabolic activity in asymptomatic females heterozygous for ornithine transcarbamylase deficiency¹⁶ have all been proposed as possible mechanisms to explain this observation in patients who have undergone diversion procedures.

Figure 3 The urea cycle: enzymes catalysing each step within the mitochondrial and cytosolic compartments are shown.

Inborn errors of metabolism highlight the important role of the urea cycle (fig 3) in the excretion of ammonia.⁴ Due to the interruption of urea synthesis hyperammonaemia occurs, together with an accumulation of other metabolic intermediaries, dependent on the point at which the biochemical pathway is blocked. Ornithine transcarbamylase deficiency is the most common of these inherited disorders and is distinguished by the high level of urinary orotic acid, occurring as a consequence of the diversion of carbamoyl phosphate via the cytosolic pyrimidine synthetic pathway.⁴ The majority of affected males present in the neonatal period and death is not uncommon before the age of 1 year. However, there are a number of reports of ornithine transcarbamylase deficiency presenting in older children or adults, including both homozygous male and heterozygous female patients.^{17–20} In the latter group, ornithine transcarbamylase enzyme activities may vary widely and symptoms often occur during periods of physiological stress—for example, childbirth, postoperatively, or during infective illnesses. Older patients have an increased likelihood of dying at presentation, often due to delays in diagnosis.²¹ In most cases, hyperammonaemia presents without evidence of substantial hepatic dysfunction.^{4 18 20}

The clinical features of hyperammonaemia are very variable and often episodic. Subtle personality changes, confusion, irritability, ataxia, or visual disturbances may be early signs. Vomiting, lethargy, and hyperventilation are alternative presenting features. Early recognition is often difficult and because of this cases present to a wide range of specialties and may go undiagnosed. Untreated hyperammonaemia can lead to raised intracranial pressure, seizures, coma, and eventually death. Particular attention should be paid to whether there have been previous episodes or a family history of similar symptoms. Recognition in the history of factors which may predispose to hyperammonaemia (table 1) may also aid early diagnosis.

Routine investigations are often unhelpful and measurement of blood ammonia levels is the key to early diagnosis. Although values

greater than 150 $\mu\text{mol/l}$ are usually seen in encephalopathic patients, blood levels do not always correlate with the clinical grade of encephalopathy. Interpretation of the result should therefore take into account the clinical state of the patient as well as the results of other investigations, including a full metabolic screen if an inherited error of metabolism is suspected. Non-haemolysed, heparinised venous samples processed rapidly in the laboratory give optimal results avoiding inaccuracies due to sample storage. Reliable measurements using a specific ion selective electrode system or an automated enzyme method are available in most biochemical laboratories.²² Blood ammonia levels can be used subsequently to monitor the response to treatment once a diagnosis of hyperammonaemia has been established, with clinical improvement usually paralleling decreasing levels. Investigation of underlying hepatic function or associated acid-base disturbance, for example, hyperchloraemic alkalosis in patients with urinary diversions, is helpful. Electroencephalography features may suggest a diffuse encephalitis or show evidence of epileptiform activity. Computed tomography or MRI brain scans may reveal cerebral oedema, though this is not a constant finding.^{9 11} Astrocyte swelling, with high astrocyte glutamine concentrations, demonstrable in experimental hyperammonaemia, may act osmotically to produce cerebral oedema. Raised glutamine concentrations in the CSF have also been recorded.⁴

Establishing the underlying cause is vital in preventing further episodes and planning definitive procedures to reverse causative factors. Such intervention is potentially curative. During the diagnostic work-up, general measures are employed to reduce hyperammonaemia as in the management of hepatic encephalopathy. Short term restriction of dietary protein, or substitution of animal for vegetable protein sources and the use of non-absorbable disaccharides, for example, lactulose and lactitol (acting by their osmotic cathartic action) reduce the dietary and endogenous nitrogen load from the intestinal lumen.² Endogenous protein breakdown may be further suppressed by a high oral carbohydrate intake or using intravenous 10% to 20% dextrose with insulin, if needed, to control blood glucose concentrations. Antibiotic treatment, for example, neomycin or metronidazole, may be particularly effective when infection with urea-splitting bacteria is suspected. Adequate supportive care, including ventilation if coma develops, is essential to provide time to clarify the underlying pathophysiology. For patients with ornithine transcarbamylase deficiency, sodium benzoate may be beneficial. Given orally or intravenously, it is excreted as its glycine conjugate, hippuric acid, increasing nitrogen excretion. Sodium phenylacetate may also be effective.⁴ In cases resistant to treatment haemodialysis has been successful.²¹ Care should be taken in the hyperammonaemic patient with seizures secondary to raised intracranial pressure as certain antiepileptic drugs, for example, sodium valproate, may

worsen hyperammonaemia and are best avoided.²³

The identification of an underlying genetic cause has important implications. Where a case of ornithine transcarbamylase deficiency has been identified, screening allows the detection of affected males and carrier females within the family pedigree. Allopurinol causes greater urinary excretion of orotic acid and orotidine in carrier females than normal and forms the basis of a cheaper, acceptable biochemical test of heterozygosity; however it may fail to identify some carriers. Enzyme assays performed on liver biopsy samples, linkage analysis or searches for specific mutations in the ornithine transcarbamylase gene on the X chromosome may also be used.⁴ Once recognised, late onset forms of the urea cycle diseases carry a better prognosis—largely due to the initiation of preventative measures and earlier recognition of exacerbations. Maintenance treatment between encephalopathic episodes involves dietary protein restriction, and rarely the need for sodium benzoate.

Non-hepatic hyperammonaemia poses a clinical challenge. A high index of suspicion given unexplained neurological symptoms in a patient with no history of liver disease should lead to the diagnosis being considered as many cases will respond to specific treatment with a favourable outcome.

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