Hyperammonaemic coma without hepatic failure

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Abstract - Although hyperammonia caused by hepatic failure is a well-known cause of coma, it is less well described in the absence of detectable liver dysfunction. We describe a case of a 54 year old woman with a decreased level of consciousness in the presence of hyperammonaemia. Laboratory studies showed normal coagulation and liver enzyme tests. In retrospect she suffered from memory- and concentration problems, somnolence, frequent vomiting and headaches. She underwent an ureterosigmoidostomy in childhood for a congenital bladder abnormality. With ureterosigmoidostomy large amounts of urea are in contact with the large bowel and its bacterial contents. Ammonia can be produced by urea-splitting bacteria, which can be present in the diversion. Due to bacterial overgrowth, especially with urease producing gram negative bacilli, hyperammonaemia can occur. We provide an overview of non hepatic causes of hyperammonemic coma and discuss therapeutic options. Initially our patient received a common treatment including protein restriction and lactulose. she also received sodiumbenzoate and carnitine for a short period of time. After being discharged from the ICU she suf-fered from relapses, which only ended when her ureterosigmoidostomy was converted into a Bricker-type ureteroileostomy.

Keywords - ammonia, coma, ureterosigmoidostomy, urea cycle

Introduction
Patients with altered consciousness are frequently admitted to the ICU. In most cases the underlying cause is readily apparent. In the presence of hepatic failure, hyperammonaemia is a recognized cause of encephalopathy. Non-hepatic causes are rare and represent a wide range of etiologies. In this article we describe a patient with a decreased level of consciousness due to hyperammonaemia without evidence of hepatic failure. We discuss the possible underlying etiologies and the most appropriate therapy.

Case report
A 54-year-old woman was referred to a hospital in the Netherlands with a decreased level of consciousness of unknown cause. One day prior to admission she had felt unwell, was unable to stand on her feet, kept repeating sentences and had an altered consciousness. Her previous medical history was unremarkable except for the construction of an ureterosigmoidostomy in childhood because of a congenital anomaly of the bladder.

On further investigation, the patient had suffered from memory and concentration problems for decades, readily falling asleep, vomiting once a week and having frequent headaches. There was no reason to suspect intoxication and apart from acetaminophen she did not take prescription medication.

On clinical examination she was fully awake, although she sometimes responded inappropriately. She could not accurately follow a finger with her eyes and was unable to comprehend what she was doing wrong. Her motor function was normal and there was no nuchal rigidity. Both pupils were isocore and responded to light. On admission her blood pressure was 195/133, but this later decreased spontaneously to 150/100 mmHg.

A computer tomogram (CT) of the brain was normal. During the next few hours her level of consciousness decreased to a Glasgow Coma Scale (GCS) of 6 with left lateralization. Her pupils were slightly dilated but still reacted normally to light. A repeated CT-scan again showed no abnormalities. Acyclovir and dexamethasone were started. Lumbar punction and magnetic resonance imaging of the brain were subsequently normal. The next day she was intubated and transported to the UMC St Radboud.

On arrival the propofol medication was stopped. Her GCS was 5 at this time. A repeated CT-scan of the brain showed no signs of haemorrhage or infarction. Blood tests revealed a serum ammonia of 153 mmol/l in the presence of normal coagulation and liver enzyme tests. The electroencephalogram did not show any seizures, but showed severe encephalopathic changes with triphasic waves consistent with metabolic encephalopathy. Treatment was started with lactulose and sodium benzoate and protein intake was temporarily discontinued. While awaiting test results the patient briefly received carnitine for a possible inborn error of fatty acid oxidation.

Three days after admission her ammonia level had decreased and she improved to a maximal level on the GCS. Amino acid analysis of the serum showed no indication of a known metabolic disorder, especially no defect of the urea cycle. There was also no evidence of any other metabolic disorder after extensive screening of the urine. A urine culture could not be obtained because of faecal contamination due to the ureterosigmoidostomy. Blood cultures were negative.

A few weeks after discharge from the ICU the patient was readmitted to the hospital twice because of decreased consciousness and high ammonia levels. Subsequently, the ureterosigmoidostomy
was converted into a Bricker-type ureteroileostomy. Following this procedure, the patient had no more relapses.

**Discussion**

**Hyperammonaemia**

The signs and symptoms of hyperammonaemia include respiratory alkalosis, vomiting, irritability, lethargy progressing to coma, seizures and apnoea. Generally, blood ammonia levels poorly correlate with the degree of encephalopathy.

When the liver is unable to metabolize all ammonia in the body (Figure 1), its elimination depends on the kidney, the muscles and the brain. In the brain, excess ammonia is detoxified to glutamine by glutamine synthase present in astrocytes, increasing intracellular osmolarity and intracellular volume. This results in cerebral oedema and increased intracranial pressure. [1,2] Albrecht and Norenberg [3] have proposed that glutamine does not cause neurotoxicity by acting as an osmolyte, but through the action of mitochondrial phosphate-activated glutaminase in astrocytes, thereby generating very high levels of ammonia in mitochondria. This leads to the generation of reactive oxygen species and mitochondrial permeability transition.

**Hyperammonaemia without hepatic failure**

The ammonium (NH$_4^+$) molecule is generated during amino acid degradation. In the gut ammonium is produced as a by-product of protein digestion and bacterial metabolism. There is also evidence suggesting an important role in ammonia formation by phosphate-activated glutaminase (PAG) present in the small intestine [4,5]. PAG hydrolyses glutamine into glutamate and ammonia. It is also present in the kidney and the brain. In the kidney ammonia is essential for renal acid-base handling. The kidney can excrete ammonia and urea. Normally ammonia is detoxified to urea in the liver through the urea cycle. Ammonia can also be detoxified to glutamine by glutamine synthetase present in astrocytes in the brain and in muscle tissue. In the circulation glutamine and urea can be considered as ammonia carriers; this is in addition to the presence of free circulating ammonia.

Several mechanisms have been proposed for hyperammonaemia in the absence of detectable liver dysfunction. Hyperammonaemia may result when the production of ammonia exceeds the capacity of the liver, which may be the case in urinary tract diversion and gastrointestinal bleeding [2]. With a urinary tract diversion, an intestinal segment is interposed within the urinary tract, but retains its native venous drainage into the hepatic circulation. Ammonia is generated in the kidney, but can also be produced by urea-splitting bacteria, which can be present in the diversion. This ammonia is absorbed through the bowel segment and is delivered to the liver by the portal circulation [6]. With ureterosigmoidostomy large amounts of urea are in contact with the large bowel and its bacterial contents. Hyperammonaemia is a known complication following ureterosigmoidostomy in relation to bacterial overgrowth, especially in the presence of urease producing gram-negative bacilli. This is probably aggravated by constipation. In the literature, several other cases of hyperammonaemia that occur decades after ureterosigmoidostomy have been described. These occurred after development of slow transit constipation [7] or acute rectocolitis [8] but also with no obvious precipitating factors [9,10].

Possible other etiologies of hyperammonaemia include disorders of the urea cycle, other metabolic causes (distal renal tubular acidosis, hyperinsulinaemic hypoglycaemia, primary carnitine deficiency, fatty acid oxidation defects), drugs (e.g. sodium valproate [11,12], anaesthetics such as halothane), following chemotherapy [13], infection, Reye’s syndrome, other causes such as parenteral nutrition, and finally idiopathic causes [7] (Table 1).

Further, hyperammonaemia may also result when the nitrogen load bypasses the liver, entering directly into the systemic circulation by a portosystemic shunt [1,7].

The hyperinsulinism/hyperammonia syndrome is caused by missense mutations of glutamate dehydrogenase. It is characterized by episodes of symptomatic hypoglycaemia and usually mild elevations of the ammonia level. It is easily controlled with oral diazoxide [14].

![Figure 1. Ureumcycle](image_url)

| Table 1. Causes of hyperammonemia without liver dysfunction and their pathophysiology |
|---------------------------------|-------------------------------------------------|
| **Cause hyperammonemia without liver dysfunction** | **Mechanism** |
| urea cycle disorders | defect or deficiency of enzyme |
| urinary tract diversion, GI bleeding | production exceeds liver capacity |
| valproic acid | role urea-splitting bacteria depletion of carnitine in β-oxidation |
| primary carnitine deficiency | inhibition of urea cycle |
| hyperinsulinism/hyperammonia syndrome | missense mutations of glutamate dehydrogenase |
| Reye’s syndrome | associated with pre-existent metabolic defects, especially β- |
| portosystemic shunt | oxidation defects |
| liver is bypassed | |

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Carnitine is a non-essential amino acid that plays a central role in the energy generation of the cell by being a cofactor in the transport of long-chain fatty acids into the mitochondrial matrix. Carnitine deficiency can lead to an accumulation of unoxidized fatty acyl-CoA molecules. It has been suggested that this can inhibit the urea cycle resulting in an accumulation of ammonia [15,16]. Valproic acid is an anti-epileptic drug which can follow the same metabolic path as long-chain fatty acids do into the mitochondrial matrix, where it is β-oxidated. Also, in this process carnitine is involved. Valproic acid can deplete carnitine stores leading to a deficiency of carnitine [16]. Reye's syndrome occurs almost exclusively in children and is a potentially fatal disease. The symptoms are a fatty liver, hyperammonaemia and neurologic disturbances. It usually develops after a viral infection and is associated with the use of aspirin. Reye's and Reye's-like syndrome can be associated with pre-existent metabolic defects, especially β-oxidation defects. These affect mitochondrial function., in this context other predisposing factors for Reye like syndrome such as urea cycle disorders and carnitine deficiency are described [17].

**Therapy**

The treatment of hyperammonaemia is highly dependent on the etiology. It is preferable to eliminate the underlying cause. The common treatment includes protein restriction, lactulose therapy and hyperalimentation. Lactulose treatment has two advantageous effects. It is an osmotic purgative and it lowers gastrointestinal pH due to the production of organic acids by bacterial fermentation. The lower pH creates a hostile environment for urea-producing bacteria which can lead to reduced ammonia production.

In cases of hyperammonaemic encephalopathy following ureterosigmoidostomy, adequate drainage of the bowel segment to shorten contact time between the urine and the bowel segment and the relief of any obstruction should be performed [6], usually with lactulose treatment and with or without rectal drainage of the involved bowel segment. Any infection should be treated with the appropriate (broad spectrum) antibiotics. Discontinuation of the ureterosigmoidostomy in some cases is also recommended [7,18].

For the treatment of disorders of the urea cycle, Brusilow and colleagues suggest alternative pathway therapy by promoting the excretion of non-urea metabolites [19]. Phenylacetate and benzoate combine with the amino acids glutamine and glycine respectively, to produce phenylacetylglutamine and N-benzoglycine, more commonly called hippurate, which can be excreted in urine [20]. In addition, renal replacement therapy has been used to treat hyperammonaemia in various cases, especially in young children with inborn errors of metabolism.

**Summary**

In cases of unexplained decreased consciousness, blood ammonia levels should be checked, even when the liver function is normal and especially in a patient with a urinary tract diversion. In cases of ureterosigmoidostomy, as well as standard therapy, antibiotics should be given to reduce urease producing gram-negative bacteria. Furthermore, rectal drainage of the bowel segment should be considered. Finally, it may be necessary to revise the urinary tract diversion.

**Article in journals:** Calandra T, Cometta A. Antibiotic therapy for gram-negative bacteremia. Infect Dis Clin North Am 1991;5:817-34

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**References**