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REVIEW

Hyperammonaemia: review of the pathophysiology, aetiology and investigation

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Summary

Acute hyperammonaemia is a medical emergency as it can progress to cerebral oedema, seizures, coma and death. Hepatic encephalopathy secondary to cirrhotic disease or portosystemic shunting are relatively well-known causes, but non-cirrhotic aetiologies of acute hyperammonaemia are less well-known, especially in the emergency department. However, an elevated ammonia is not required to make the diagnosis of hepatic encephalopathy. Although measurement of plasma ammonia is recommended for patients with acute, unexplained, altered mental status, as early identification allows early effective management which may prevent irreversible brain damage, there is currently reduced awareness among physicians of the non-cirrhotic aetiologies of acute hyperammonaemia. Furthermore, measurement of ammonia in patients with cirrhosis has been shown to have low sensitivity and specificity, and not to have altered management in the majority of cases; thus, measurement of ammonia is currently not recommended in guidelines for management of hepatic encephalopathy.

We sought to describe the pathophysiology of hyperammonaemia and review the non-cirrhotic causes. This was achieved by review of MEDLINE, PubMed and Web of Science databases to include published English literature within the last 20 years. We also present a framework for investigating the acute non-cirrhotic causes of hyperammonaemia to assist both chemical pathologists and clinicians managing these often challenging cases.

Key words: Hyperammonaemia; ammonia; non-cirrhotic; aetiology.

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INTRODUCTION

Ammonia is a potent neurotoxin that can cause a metabolic encephalopathy requiring urgent diagnosis and management.[1–3] Acute hyperammonaemia is defined as an elevated plasma ammonia concentration and is associated with a heterogenous clinical spectrum. In adults, this ranges from loss of appetite and vomiting to altered mental status, seizures and coma.[2] Hyperammonaemia is a medical emergency with high morbidity and mortality where the total duration and extent of hyperammonaemia negatively correlate with neurological outcome.[2] Thus, early recognition and management can be life-saving and prevent permanent brain damage.[1,2,4] All patients presenting with unexplained altered mental status should undergo prompt measurement of ammonia concentration.[1–3] The aetiology of hyperammonaemia in adults is related to severe liver disease in ~90% of cases.[3] Non-cirrhotic hyperammonaemia arises from either increased ammonia production or decreased ammonia elimination, and is very likely under recognised. Precipitants include infection, drugs and inherited metabolic disorders.[3,4]

This review focuses on the pathophysiology, aetiology and diagnostic work-up for non-cirrhotic hyperammonaemia and is aimed to be a resource for emergency, general and intensive care physicians, as well as chemical pathologists.

PATHOPHYSIOLOGY OF HYPERAMMONAEMIA

Measurement of ammonia

Automated enzymatic assays are frequently used to measure ammonia, for example using the enzyme glutamate dehydrogenase:

$$\text{Ammonia} + \alpha\text{-ketoglutarate and nicotinamide adenine dinucleotide + hydrogen (NADH)} \xrightarrow{\textit{glutamate dehydrogenase}} \text{glutamate and NAD+}$$

The reduction in NADH absorbance at 340 nm is proportional to the ammonia concentration.[5] Lactate dehydrogenase is often added to reduce pyruvate and remove this interference. Accurate determination of ammonia concentration requires correct collection and handling of specimens to avoid artefactual rises *in vitro*.[6,7] Haemolysis is a source for falsely elevated ammonia as ammonia is three-fold higher in

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erythrocytes than in plasma.[8] Deamination of plasma and cellular proteins also continues to occur *in vitro* and is correlated with high gamma-glutamyl transferase (GGT) activity.[8,9] To reduce these preanalytical factors, a free-flowing venous (or arterial) blood sample without torniquet should be collected into a tube containing anticoagulant.[2,9,10] EDTA has been recommended as the preferred anticoagulant rather than sodium heparin or sodium fluoride/potassium oxalate because of risk for non-specific sample-buffer interactions.[9,11] The sample should be immediately placed on ice in order to limit *in vitro* deamination and analysed within 60 minutes.[2,8,11] Transport by foot or pneumatic tube does not appear to affect the integrity of the sample.[9] Centrifugation at 4°C is also recommended.[12]

Ammonia production

All tissues in the body produce ammonia.[13] The main source of ammonia production is the gastrointestinal tract where it is a by-product of protein digestion and bacterial metabolism.[3,14] The portal vein has an ammonia concentration 5–10-fold the systemic circulation. Renal sources of ammonia stem from its involvement in acid-base handling where it facilitates proton excretion and the regeneration of bicarbonate.[14] Ammonia is synthesised from glutamine in the proximal tubule and increases with gastrointestinal bleeding and acidosis. Skeletal muscle is also a source of ammonia and production escalates during seizures or intense exercise.[4,14]

Transamination of amino groups from proteins produces glutamate, which undergoes oxidative deamination to produce ammonia. Ammonia exists in both an ionised and unionised form by means of a buffering reaction:[13,15] $NH3 + H+ \rightarrow NH4+$.

The pKa (negative log of the acid dissociation constant) for ammonium is ~9.15, which is the pH at which there are equal amounts of both ionised (NH4+) and non-ionised (NH3) forms. Under physiological conditions, where pH values are less than 9.15, the protonated form is favoured, and the majority of 'ammonia' exists as ammonium.[13,15] The terms ammonia and ammonium are often used clinically (albeit erroneously) interchangeably. However, to avoid clinical confusion, this review will use 'ammonia' to refer to both ammonia and ammonium.

Ammonia degradation

Ammonia degradation occurs primarily in the liver, with the majority occurring on first pass through the liver.[4] It is metabolised to urea via the urea cycle, which comprises six enzymatic reactions. These reactions occur either in the mitochondria or cytosol within hepatocytes.[14] The first step is also the rate-limiting step and involves conversion of ammonia and bicarbonate to carbamoyl phosphate which is catalysed by the enzyme carbamoyl phosphate synthetase I (CPS1). CPS1 requires activation from N-acetyl-glutamate, an allosteric effector that is synthesised from glutamate and acetyl-CoA, catalysed by N-acetylglutamate synthase (NAGS), which is upregulated by arginine.[14,16]

Carbamoyl phosphate is combined with ornithine to form citrulline via ornithine transcarbamylase (OTC). Citrulline then reacts with aspartate to form argininosuccinate catalysed via argininosuccinate synthetase. Argininosuccinate is converted into arginine via arginosuccinate lyase, which subsequently undergoes hydrolysis via arginase 1 to form urea and ornithine. The regenerated ornithine can then be recycled back into the urea cycle.[17] This series of metabolic reactions is demonstrated in Fig. 1.

Ammonia detoxification can also occur via hepatic glutamine metabolism. Glutamine is synthesised by the glutamine synthetase (GS)-catalysed ATP-dependent reaction of glutamate with ammonia.[15] This process is restricted to perivenous hepatocytes which scavenge excess ammonia not used in the synthesis of urea.[14,15] It is independent of the urea cycle. There is no difference in the percentage of ammonia detoxification by either hepatic glutamine synthetase or the urea cycle; both pathways contribute ~35% for ammonia clearance in GS knockout mice.[17] Dysfunction of the GS pathway and failure of these scavenger cells, such as from hepatic injury, can thus result in hyperammonaemia.[14]

Urea elimination occurs primarily via the colon and kidneys.[3,16] When hepatic metabolism is overwhelmed or ammonia bypasses the liver, such as through portosystemic shunting, systemic ammonia rises and its elimination shifts to the kidney, skeletal muscle and brain.[3,4,18] Ammonia that reaches the brain is metabolised to glutamine by astrocytes. Subsequent deamination of glutamine produces the neurotransmitter glutamate.[4,10] However, astrocytes have only a limited ability to protect the brain from increased ammonia entering the brain from the circulation, as at physiological conditions they are at near maximal ability to synthetise glutamate.[10] Similarly, ammonia is taken up by skeletal muscle and metabolised into glutamine. Ammonia excretion in the kidneys can be upregulated by as much as 70%.[3]

The exact pathogenesis of ammonia neurotoxicity is unclear.[3] Ammonia is thought to interfere directly with neuronal function. Astrocytes rapidly metabolise ammonia to glutamine. The subsequent rise in glutamine results in increased intracellular osmolarity leading to oedema.[4] This triggers an inflammatory cascade, leading to oxidative stress and apoptosis.[3,4] Additionally, ammonia-induced glutamate release and impaired clearance of glutamate causes overstimulation of N-methyl D-aspartate (NMDA) receptors. An increase in the synthesis of nitric oxide leads to intracerebral vasodilation and increased intracranial pressure. Lastly, hyperammonaemia results in increased cerebral uptake of amino acids and disrupts synthesis of neurotransmitters dopamine, norepinephrine and serotonin.[3] In summary, hyperammonaemia results in cerebral oedema and loss of cerebral autoregulation leading to increased intracranial pressures, herniation and seizures.[4]

AETIOLOGY AND UNDERLYING MECHANISMS OF NON-CIRRHOTIC HYPERAMMONAEMIA

The aetiology of non-cirrhotic hyperammonaemia is extensive and can be largely categorised into: (1) increased ammonia production often in the presence of an underlying metabolic defect or other secondary cause, and (2) decreased ammonia elimination (Table 1).

Infection

Non-cirrhotic hyperammonaemia can be caused by infection by urease producing bacteria within the genitourinary tract.

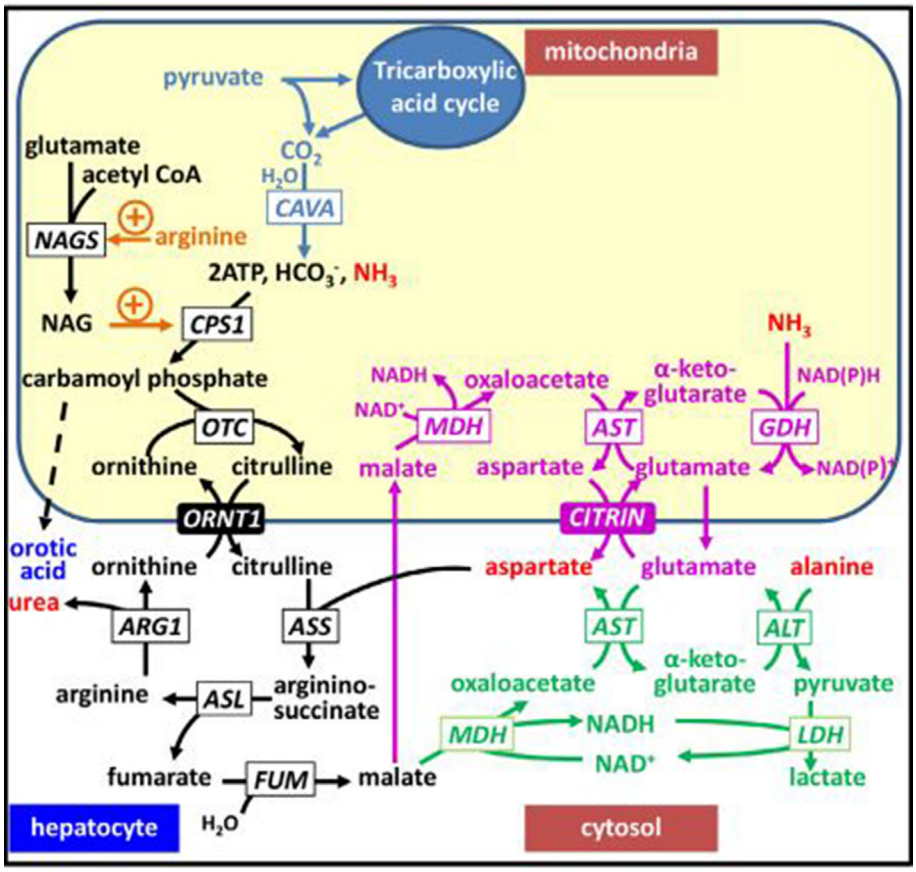

Fig. 1 Core components of the urea cycle. The main route of ammonia detoxification occurs through the urea cycle. Firstly, ammonia is converted to carbamoyl phosphate by carbamoyl phosphate synthetase I (CPS1) which requires N-acetylglutamate (NAG). The second step sees carbamoyl phosphate combined with ornithine to form citrulline via ornithine transcarbamylase (OTC). Arginosuccinate results from the reaction between citrulline and aspartate which is catalysed by argininosuccinate synthetase (ASS). Arginosuccinate is converted to arginine which is metabolised to urea by arginosuccinate lyase (ASL) and arginase (ARG), respectively. Reproduced with permission from Häberle *et al.*[7]

Cases have also been reported from surgical mesh infections and colitis.[3,19,20] Infection-induced non-cirrhotic hyperammonaemia has occurred in young children with congenital defects of the urinary tract, the elderly and the immunocompromised. It is also a rare complication in patients with ureterosigmoidostomy.[3,10] In urinary tract infections, the enzyme urease hydrolyses the urea in urine to ammonium. Alkalinisation of the urine leads to ammonium ions becoming lipophilic ammonia. Urinary ammonia is then absorbed by the vesical venous plexus and enters the systemic circulation via the inferior vena cava.[3,21–24] Cases have been reported of non-urease-producing organisms also causing

Table 1 Aetiology of non-cirrhotic hyperammonaemia

Increased ammonia production	Decreased ammonia elimination
Infection from urease-producing organisms [a]	Inborn error of metabolism[b]
Protein load [c] and increased catabolism	Urea cycle defects
Seizures	Fatty acid oxidation disorders
Severe exercise	Organic acidurias
Very high protein diet	Methylmalonic aciduria
Trauma	Propionic aciduria
Starvation	Maple syrup urine disease
Total parenteral nutrition	Hyperinsulinism hyperammonaemia syndrome
Upper gastrointestinal bleeding	Drugs[d]
Haemato-oncological disorders: multiple myeloma, bone marrow transplantation, chemotherapy	Porto-systemic shunts
Gastric bypass	Renal tubular acidosis
Drugs [d]	

[a] Urease-producing organisms are common culprits underlying non-cirrhotic hyperammonaemia, although non-urease-producing bacteria causing hyperammonaemia have also been reported.
[b] Some of the more common inborn errors. There are others that cause hyperammonaemia.
[c] Significant hyperammonaemia may occur if the person has an underlying predisposition such as a urea cycle defect or metabolic disorder, which may be undiagnosed.
[d] Drug-induced hyperammonaemia can cause either increased production or decreased elimination of ammonia.

hyperammonaemia from elevated intravesical pressures caused by urinary retention or obstruction.[21–25] Systemic infections of ureaplasma and mycoplasma in heart-lung transplant recipients are rarer cases of hyperammonaemia as well as herpes simplex infections in neonates.[3,26]

A list of urease-producing organisms identified in hyperammonaemia include:[3,10,19–27] *Proteus mirabilis*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Corynebacterium* species, *Staphylococcus aureus*, *Providencia rettgeri*, *Morganella morganii*, *Ureaplasma* species and *Mycoplasma hominis*. Non-urease-producing organisms include:[24,27,28] *Escherichia coli*, *Enterococcus faecalis*, *Streptococcus agalactiae*, *Staphylococcus epidermidis* and *Cryptococcus neoformans*.

Drug-related causes

Drug-induced hyperammonaemia is often caused by disruption of the urea cycle or enhanced release of ammonia from the kidneys. The following drugs are implicated in hyperammonaemia (see also Table 2).

Valproic acid

Valproic acid (VPA) is the most well-known drug to cause hyperammonaemia with an estimated prevalence of 35–45%.[3] It is a branched short-chain fatty acid that is hepatically metabolised via a combination of glucuronide conjugation and mitochondrial beta oxidation.[29] Multiple mechanisms for VPA-induced hyperammonaemia have been proposed and include direct inhibition of N-acetyl glutamate, carnitine depletion, blockage of calcium and sodium channels and enhanced GABAnergic transmission.[1,29–31] VPA-induced hyperammonaemia does not correlate with dosage, duration or VPA level.[3,31–36] There are reported cases of VPA-induced hyperammonaemia of 500–3000 mg daily dosing, often with normal VPA levels and duration of use from within 24 hours to >2 years later.[1,3,29,34–37] Risk factors for VPA-induced hyperammonaemia include increased age, carnitine deficiency and concurrent use of other anti-epileptic and anti-psychotic agents, in particular phenytoin and risperidone.[31,32,36,38] Carnitine is important for the metabolism of VPA. Deficiency is either primary (genetic) or secondary and includes acquired medical conditions such as chronic renal failure, malignancy and malabsorption syndromes (inflammatory bowel disease, coeliacs).[33,34,38] Concomitant use of other medications, 'hepatic inducers' such as phenytoin, phenobarbital and carbamazepine, may increase VPA metabolism, leading to increased formation of metabolites such as propionate and 4-en-VPA, which inhibit CPS1 and increase ammonia levels.[13,30–32,34,35,38] The mechanism for risperidone interaction with VPA is not well established and may induce VPA-ammonia toxicity by displacing VPA from protein to the blood. However, hyperammonaemia is not induced by risperidone alone.[39] It is also possible the use of VPA may expose a patient with previously subclinical urea cycle defect (UCD), so careful investigation needs to be conducted.[40]

Table 2 List of drugs causing hyperammonaemia

Drug	Dosage range	Time to onset to symptoms
Valproate	500–3,000 mg	24 hours to >2 year
Carbamazepine	>600 mg	2 days to 1 month
5-fluoro-uracil	1,000–2,600 mg/m^2	0.5–5 days
Asparginase preparations	2,500 units/m^2[a] 25,000 units/m^2[b]	1–10 days
Steroids	Standard[c]	5 days
Methamphetamines	–	Hours to 1 week[d]
Aspirin	45 mg/kg	>5 days
Glycine	≥24 L	Minutes to hours
Total parenteral nutrition	–	Unclear
Sulfadiazine/ pyrimethamine	1.5 g/75mg	≤10 days
Glufosinate containing herbicide	>13.9 g	4–60 hours

The inclusion of a dose range and time to symptom onset has been based on data collected from case reports.
–, no clear dose identified in available literature.
[a] Asparginase based preparations included pegaspargase.
[b] Erwinia asparginase.
[c] Hyperammonaemia developed post-treatment dose steroid administration; assumption thus made that these would be 'standard' treatment related doses according to their indication.
[d] Drugs of abuse are difficult to quantify and time to onset presumed within hours to one week based on positive urine drug test which can remain positive up to one week post-drug administration.

Carbamazepine

There have been several case reports describing carbamazepine-induced hyperammonaemia.[41,42] This has occurred in the setting of increased dose or the addition of carbamazepine to other anti-epileptic drugs (not including VPA). Dose increases above 600 mg and normal therapeutic levels have been reported with an onset of symptoms between 2 days and 1 month. The underlying mechanism is similar to VPA and involves disruption of the urea cycle.[41,42]

Hyperammonaemia from olanzapine use has been described in a single case report, but the exact mechanism is unknown.[43]

Fluoropyrimidines

These include 5-fluoro-uracil (5-FU) and pro-drugs S-1, capecitabine and tegafur-uracil. They are chemotherapeutic agents used to treat gastrointestinal, head, neck and ovarian malignancies.[44–47] Acute hyperammonaemic encephalopathy is a rare but serious side effect of treatment with fluoropyrimidines. The most cited in the literature is 5-FU with a prevalence of 5.7–8.7% with high dose infusions (2,600 mg/m^{2}over 24 h) and is rarely prescribed.[44–47] However, typical doses between 1,000 and 1,200 mg/m^2 have also been reported in cases and case series as causing hyperammonaemic encephalopathy with onset of symptoms occurring between 0.5 and 5 days.[1,44,45,47] The proposed mechanism of action is accumulation of 5-FU metabolite fluorocitrate, which inhibits the Krebs cycle and impairs ATP-dependent urea cycle leading to ammonia accumulation. 5-FU toxicity can be aggravated by infection, dehydration, constipation, renal dysfunction and weight loss.[44,45]

Asparaginase

Asparaginase is a chemotherapeutic agent used in the treatment of acute lymphoblastic leukaemia. It induces cellular apoptosis via inhibition of protein synthesis by depleting asparagine levels. Asparaginase hydrolyses asparagine to

aspartic acid and ammonia, where excessive generation of ammonia can overwhelm endogenous metabolism leading to hyperammonaemia.[48–50] The incidence is unknown and can occur between 1 and 10 days following asparaginase administration. Ammonia toxicity appears to gradually accumulate with successive doses of treatment due to the long half-life of asparaginase, where ammonia levels may not normalise before the next dose.[48–50] Observations suggest a correlation between ammonia levels and triglyceride values as an indicator for toxicity.[49]

In regard to other chemotherapeutic agents, high dose IV rituximab has been reported to cause hyperammonaemia, usually through unmasking of an underlying UCD.[51,52]

Steroids

There are at least five case reports that have reported steroid-induced hyperammonaemia encephalopathy.[53–57] The onset of symptoms is generally around 5 days following steroid administration, and all occurred in adult patients with late-onset OTC deficiency. No doses were reported, although steroids were presumably administered at standard treatment doses based on indications (i.e., betamethasone for pre-term labour). Steroids have a catabolic effect with the increased protein turnover leading to increased endogenous release of nitrogen and hyperammonaemia.[53–57]

Methamphetamines

A single case series has reported hyperammonaemia in methamphetamine abuse in three patients. One case had mild hepatic dysfunction without synthetic involvement.[58] Clinical *in vitro* and *in vivo* studies show methamphetamine-induced neurotoxicity (aside from direct neuronal effects) may be mediated in part by peripherally derived ammonia from methamphetamine-induced renal damage, rhabdomyolysis and hepatic damage. This can be exacerbated with comorbid alcoholic cirrhosis and viral hepatitis/human immunodeficiency virus.[59] Studies in rats have shown methamphetamine-induced neurological effects can be ameliorated by co-administration with lactulose to reduce plasma and brain ammonia.[60] However, the psychotic effects of methamphetamines cloud the significance of elevated ammonia in this patient group and may be an incidental rather than causative finding for altered mental status. Nevertheless, given the multiple organ effects, a consideration for methamphetamines in hyperammonaemia still warrants mention. Time to symptom onset is unclear given unknown drug use times; urine drug testing is also unreliable.

Aspirin

Reye syndrome is a rare complication of aspirin treatment. It is characterised by acute encephalopathy and hepatic dysfunction and is predominantly seen in children and young adults <18 years following ingestion during a viral prodrome.[61] It is a biphasic illness with initial viral prodrome lasting a few days followed by 1–5 days of remission. Acute onset of symptoms of Reye syndrome follows thereafter. Earlier studies suggested a dose response effect; however, doses of <45 mg/kg have also been implicated.[61,62] Following government recommendations against aspirin use in children, the incidence of Reye syndrome has significantly decreased and now occurs very infrequently leading some to question the diagnosis. There are also increased awareness and diagnosis of UCDs which share similar features to Reye syndrome presentation. The underlying mechanism is unclear and has been proposed to be due to salicylate-induced mitochondrial dysfunction and reduced activity of the urea cycle by NAG depletion and fatty acid oxidation.[13,61,62] Co-administration of aspirin with VPA or acetazolamide leading to hyperammonaemia has been described in more recent case reports.[63,64] Aspirin is highly protein bound as well as a nephrotoxic. It may potentiate the effects of co-administered drugs and reduce the renal excretion of ammonia leading to hyperammonaemia encephalopathy.[63]

Glycine

Irrigation absorption syndrome occurs when large amounts of glycine, often used as an irrigation fluid in surgeries [especially transurethral resection of the prostrate (TURP)] are systemically absorbed (≥24 L). Glycine is metabolised to pyruvate with release of ammonium ions. Symptom onset is minutes to hours post-procedure, with an incidence of 2% in TURPs.[65]

Total parenteral nutrition (TPN)

High protein nutritional supplementation has been reported to cause hyperammonaemia in the settings of: (1) neonates due to metabolic immaturity and reduced tolerance to excessive amino acid intake; (2) hyperalimentation; and (3) in patients with undiagnosed UCDs leading to first presentation of acute decompensation.[66,67] High protein dietary supplements in cases of anorexia have also been reported to cause hyperammonaemia.[68] The pathophysiology may be similar to refeeding syndrome and may be due to reduced urea cycle activity (namely glutamine synthetase) and nitrogen challenge from refeeding leading to hyperammonaemia.[67]

Sulfadiazine and pyrimethamine

Historically, antibiotics sulfadiazine and pyrimethamine have been described in a single case report to cause hyperammonaemia considered to be due to antibiotic-induced carnitine deficiency.[69] No recent cases of hyperammonaemia from these agents has been reported in the literature. It is possible an alternate cause such as underlying UCD may have been present in this case.

Glufosinate (GLA)-containing herbicides

The mechanism for GLA-related neurotoxicity is unclear. It has been proposed to cause an imbalance between glutamate and glutamine, as well as possible glutamine synthase inhibition resulting in hyperammonaemia.[70] Onset of neurotoxicity is delayed and occurs between 4 to 60 hours post-ingestion.[71] Peak ammonia levels above 53 μmol/L (90 μg/dL) are thought to be predictive for neurotoxicity and >88 μmol/L (150 μg/dL) predictive of in-hospital mortality. However, the time to ammonia level and onset of symptoms is not well established with small centred studies recommending ammonia level 'within 12 hours' of emergency department presentation.[71,72] Higher ingested amounts increase risk for neurotoxicity, with one study estimating ingestion of >13.9 g as a predictor of poor prognosis.[73] Other predictors for high morbidity and mortality include elderly patients >70 years, Glasgow Coma Scale <9 at triage, and absence of concomitant alcohol consumption.[73,74]

Disease/organ-related causes

Haematological malignancies

Increased ammonia production leading to altered sensorium is a rare but documented cause of non-cirrhotic encephalopathy in patients with haematological malignancies.[3,75,76] The exact mechanism is unknown, but is likely multifactorial and involves infection with urease-producing bacteria, transient impairments affecting the urea cycle, increased protein catabolism, gastrointestinal bleeding and pharmacological effects of chemotherapeutic agents.[3] The estimated incidence of hyperammonaemia in multiple myeloma is 3.8%.[76] Advanced stage of myeloma, IgA subtype and the appearance of myeloma cells in the peripheral blood are risk factors for development of hyperammonaemia.[75,77–79] Excessive ammonia production by myeloma cells from amino acid metabolism, liver infiltration leading to formation of systemic-portal shunts and interference with urea metabolism are proposed mechanisms for hyperammonaemia in multiple myeloma.[75,77] In patients receiving intensive chemotherapy, an 'idiopathic hyperammonaemia' has been described and occurs within a few hours to days from the commencement of therapy.[3,77] It has also been observed in patients undergoing bone marrow transplantation between 15 and 100 days post-transplant.[80]

Bariatric surgery

Gastric bypass-related hyperammonaemia is a rare but increasingly recognised entity with an estimated 50% mortality rate.[81,82] It has a variable time to onset from one month to 28 years and a predilection for women.[81] Hyperammonaemia, hypoalbuminaemia, hypoglycaemia, elevated plasma glutamine, low zinc and other nutritional deficiencies are hallmark features of this condition.[81–83] Various mechanisms have been proposed and include alterations in the intestinal microbiome, impaired function of the urea cycle, heightened catabolic state and unmasking of long standing previously asymptomatic UCDs.[82,84]

Gastrointestinal bleeding

Large gastrointestinal haemorrhage causing hyperammonaemia typically occurs in the setting of cirrhosis or hepatic impairment, porto-systemic shunting and underlying UCDs. Increased ammonia production has also been attributed to increased renal ammoniagenesis and protein degradation by colonic flora.[85] It has an estimated 6% incidence in one large study of intensive care unit patients without hepatic impairment.[86]

Distal renal tubular acidosis

Distal renal tubular acidosis (RTA) is more commonly reported in children and hypothesised to be due to an imbalance between renal ammoniagenesis and impaired ammonia excretion in response to metabolic acidosis.[87,88] Hyperammonaemia in distal RTA in an adult with hyperparathyroidism has been described in one case report.[89]

Skeletal muscle

Pathologies affecting skeletal muscle can also result in hyperammonaemia and are seen in intense physical activity, seizures (in particular status epilepticus) and trauma.[3,77] Although skeletal muscle is normally a net consumer of ammonia, excess production can saturate glutamine synthetase activity resulting in increased ammonia levels.[90] Decompensation and symptomatic hyperammonaemia normally occurs in patients with concurrent hepatic impairment or UCD, where the increased nitrogen load cannot be adequately cleared.[77,90] However, cases of symptomatic hyperammonaemia from intense muscle activity alone have been described in case reports.[90] Hyperammonaemia secondary to seizures is transient and usually rapidly normalises within 8 hours.[18,91] Ammonia concentrations range from 67 µmol/L to 537 µmol/L.[91] Paradoxically, ammonia can cause seizures and caution should be used when identifying hyperammonaemia as either precipitant or secondary to seizures.

Inborn errors of metabolism

Inborn errors of metabolism (IEM) include UCDs, organic acidurias, defects in beta-oxidation of fatty acids causing carnitine deficiency, dibasic aminoaciduria and defects in pyruvate metabolism.[3,4] The majority of IEM are diagnosed in the early neonatal period or childhood.[77] However, newborn screening will not detect all of these, especially CPS1 or OTC deficiency. Partial deficiencies are often not detected during neonatal screening and present later in life as recurrent hyperammonaemic crises seen across a variable clinical spectrum of presentations. They are being recognised more commonly in adults, thus an awareness of IEMs in this age group is pertinent to achieving positive outcomes. UCDs are the most common IEM with an estimated incidence of 1:8000.[7] Any enzyme in the urea cycle can be affected, although the most common is OTC deficiency.[77] It is an X-linked disease with large phenotypic variation in both females and males, making the diagnosis difficult. Thus clinical manifestations of OTC deficiency can have late-onset and can be largely asymptomatic until a precipitating event results in symptomatic hyperammonaemia.[3,4,77,92] CPS, NAGS and citrin deficiency (Type II citrullinaemia) can also present in adulthood.[4] Precipitants include infection, VPA consumption, post-partum and post-operative stress, gastrointestinal bleeding and TPN.[3,77,92]

Organic acidurias

Organic acidurias can arise from a defect in the metabolic pathways of carbohydrate, amino acid and fatty acid oxidation. They are thus characterised by excessive accumulation of organic acid metabolites and increased urinary acid excretion. Disruption of the pathways in the urea cycle by the abnormal accumulation of these toxic metabolites can cause hyperammonaemia, similar to that seen in UCDs. The more prevalent organic acidurias are methylmalonic acidaemia (MMA), propionic acidaemia (PA) and isovaleric acidaemia.[93–95]

Propionic acidaemia

The estimated incidence of PA is between 1:3,000 (Saudi Arabia) and 1:35,000 (USA).[93] It is caused by a deficiency in the enzyme propionyl CoA carboxylase (PCC) which leads to the accumulation of toxic compound propionyl CoA. A significant amount of propionyl CoA is generated by gut bacteria. Additionally, as biotin is a co-factor for PCC function, disorders of biotin metabolism can also impair PCC activity.

Although rare as the initial presentation in adults, acute decompensations occur during times of metabolic stress. The clinical presentation includes vomiting, lethargy, seizures, pancreatitis and encephalopathy. A quarter of patients develop arrythmias (prolonged QT) from acute cardiomyopathy. A profound high anion gap ketoacidosis with normal or low glucose, elevated urinary propionate organic acid metabolites and elevated C3-acylcarnitine are diagnostic.[94,95]

Methylmalonic acidaemia

MMA encompasses a group of disorders characterised by methylmalonyl-CoA mutase deficiency resulting in elevated blood and urinary concentrations of methylmalonic acid. Cobalamin (vitamin B12) is an important co-factor, thus disorders of cobalamin metabolism or nutritional deficiencies can also result in MMA.[95,96] The estimated incidence is 1:50,000.[93] Frequently patients present with chronic renal failure. Neurological deficits such as spastic quadriparesis, progressive movement disorder and vision loss have also been described. Cardiomyopathy does not usually develop compared to PA; although similar to PA, high anion gap ketoacidosis with normal/low glucose is seen. An elevated plasma/urine methylmalonic acid, together with elevated C3 and C4-DC acylcarnitines, C3 carnitine (propionyl carnitine) is increased in both PA and MMA. C4-DC (methylmalonyl-carnitine) is increased in MMA but normal in PA.[94–96]

Fatty acid oxidation disorders

Fatty acid oxidation disorders (FAODs) arise from defects to either mitochondrial beta-oxidation or carnitine-based transport of fatty acids leading to deficient energy production.[97–99] The estimated incidence is 1:5,000 to 1:10,000 and are all inherited in an autosomal recessive fashion.[97] There are three characteristic clinical presentations: (1) acute hypoketotic hypoglycaemia with encephalopathy, hepatomegaly and liver dysfunction; (2) cardiomyopathy, arrythmias or conduction defects; and (3) myopathy, myalgia and rhabdomyolysis. Myopathic disease is the most often seen in adult acute presentations of FAODs; whilst a prominent feature in childhood FAODs, hypoglycaemia becomes less common in adulthood where there is increased fasting tolerance.[99] Hyperammonaemia can occur by disruption of the urea cycle from abnormal accumulation of fatty acids. Acylcarnitine profiling is key to diagnosing FAODs.[99] The most common FAOD is medium chain acyl-CoA dehydrogenase deficiency (MCAD). Other FAODs include very long chain acyl-CoA dehydrogenase deficiency (VLCAD), long chain 3-hydroxy acyl-CoA dehydrogenase deficiency (LCHAD), carnitine palmitoyltransferase type 1 deficiency (CPT-1) and multiple acyl-CoA dehydrogenase deficiency (MADD).[97–99]

Disorders of mitochondrial energy metabolism have an estimated incidence of 1:5,000 and are among the most prevalent of inherited metabolic diseases.[100] Clinical presentation is heterogenous and can occur at any age.

Hyperinsulinism-hyperammonaemia syndrome

Hyperinsulinism-hyperammonaemia (HIHA) syndrome arises from an activating mutation in glutamate dehydrogenase (GDH) which is involved in the oxidative deamination of glutamate to alpha-ketoglutarate and by-product ammonia.[101] Recurrent hypoglycaemia induced by fasting and protein-rich meals and hyperammonaemia are characteristic of this syndrome. Notably, ammonia can be 3–5 times the upper limit of normal, however the hyperammonaemia is frequently asymptomatic.[101]

CLINICAL PRESENTATION

Hyperammonaemia has a highly variable clinical presentation depending on age, the underlying cause and other co-morbidities.[10] Irritability, vomiting, lethargy and behavioural disturbances usually evolve over a course of hours to days. Without treatment, this can rapidly progress to seizures, coma and death.[2–4,10,102] Clinical presentation depends in part on underlying aetiology. Ataxia, recurrent falls and cognitive slowing can be seen in VPA-induced hyperammonaemia.[35] Fever and urinary retention in an encephalopathic patient may point to urease-enzyme-producing bacteria. Late-onset UCDs are often episodic and fluctuating and include headaches, recurrent abdominal pain, lethargy and vomiting.[3,102] Psychiatric manifestations such as mania, depression, anxiety and anorexia have been described in the literature as chronic manifestations of UCDs.[2,3,103] A history of protein aversion also favours this diagnosis. Ultimately, ammonia is neurotoxic, thus the principal clinical presentation will be neurological[6,7,103–105] (Table 3).

INVESTIGATION AND DIAGNOSIS

Hyperammonaemia must be considered in any patient with an unexplained altered conscious state.[2,7,104]

Laboratory investigation

Reference intervals for ammonia vary between laboratories and age groups and no consensus for the upper limit of normal has been reached within the literature. Generally, hyperammonaemia is defined as ammonia level >50 μmol/L in adults and >100 μmol/L in newborns.[2] Plasma ammonia levels >150 μmol/L are highly suggestive of an IEM.[105] Repeat testing of ammonia levels is recommended if initial ammonia level is elevated (especially if the initial value is >100 μmol/L) and should be repeated within 4 hours as levels often rapidly increase in patients with UCDs.[6,10] Interpreting ammonia levels and clinical presentation in adult patients without hepatic encephalopathy typically reveals mild symptoms such as drowsiness and tremor when ammonia levels are <100 μmol/L, confusion and behavioural disturbances when ammonia levels are between 100–200 μmol/L and significant neurological symptoms such as seizures, cerebral oedema and coma in ammonia levels >200 μmol/L.[3,4,18]

Other laboratory investigation focuses initially on excluding a hepatic source for hyperammonaemia before progressing to work-up for IEM.[4] Measuring C-reactive protein and hepatitis serology plus urinalysis should be performed. Drug levels should be considered where toxins may cause hepatic failure or induce hyperammonaemia (i.e., VPA).[2,4] Mild liver function abnormalities may be seen in patients with an IEM, although tend to regress with clinical improvement.[6] Respiratory alkalosis can be suggestive of early UCDs, whereas metabolic acidosis can then become

Table 3 Clinical presentation of non-cirrhotic hyperammonaemia

Acute ammonia toxicity	Chronic ammonia toxicity
Vomiting	Headaches
Altered level of consciousness (from lethargy to acute encephalopathy)	Intellectual disability
Ataxia	Auto-vegetarianism/protein aversion
Behavioural disturbances: hallucinations, paranoia, personality changes, agitation	Psychiatric manifestations: mania, aggression
Seizures	Recurrent abdominal pain and vomiting (may be cyclical)
Stroke-like episodes	Confusion
Asterixis	Neurological deficits: progressive diplegia, quadriplegia from childhood (HHH, arginase deficiency)

Symptoms can range from mild to severe depending on ammonia level. Levels <100 µmol/L will exhibit milder symptoms such as drowsiness and tremor. Confusion and behavioural disturbances become evident at ammonia levels between 100 and 200 µmol/L. Levels above 200 µmol/L result in seizures and coma. UCDs have both acute and chronic manifestations of ammonia toxicity. HHH, hyperornithinaemia-hyperammonaemia-homocitrullinuria syndrome.

established or be suggestive of organic acidemias.[104] Elevated urinary ketones and hypocalcaemia are also seen in the latter. Hypoglycaemia is not a feature of UCDs, but can be the predominant manifestation of organic acidurias (especially 3-HMG-CoA-lyase deficiency). Lactate is non-specific and can be normal or elevated in IEM.[6] Specialised metabolic profiling is indicated in cases where IEM is suspected and includes plasma amino acids where elevated glutamine is a feature of all UCDs. Citrulline is increased 100-fold in argininosuccinate synthetase deficiency and 10-fold in argininosuccinate lyase deficiency. Arginine is increased in arginase deficiency and reduced in most other UCDs, such as CPS1 and OTC deficiencies.[6] Low citrulline is a useful marker of OTC and CPS1 deficiencies. Urine tests include urine amino acids and organic acid analysis. Plasma acylcarnitine profile may also help guide diagnosis for fatty acid oxidation disorders and organic acidurias. Samples for these specialised tests should be taken as soon as possible (where hyperammonaemia source is not obvious) and urgently analysed within 24 hours, although results should never delay treatment.[6,7,104] The recommended tests for work-up of hyperammonaemia are outlined in Table 4.

Table 4 Diagnostic tests for hyperammonaemia

Laboratory investigations	Specialised metabolic investigations
Ammonia levels	Plasma amino acid profile
Full blood picture	Urine amino acid profile
Urea and electrolytes	Urine organic acid profile
Liver function tests	Plasma acylcarnitine profile
Calcium	
Glucose	
Lactate	
Blood gas	
Thyroid function tests	
Urinary ketones	
Urine dipstick and culture	
Toxicology screen including specific drug levels such as paracetamol, valproate, etc, where clinically indicated	

Specialist metabolic profiling should be completed in cases where an inborn error of metabolism (IEM) is suspected, although this should not delay treatment. Generally, ammonia levels >150 µmol/L are highly suggestive of IEM. Other tests are aimed at excluding other non-cirrhotic aetiologies of hyperammonaemia such as infection and drugs.

Imaging

Abdominal ultrasound, computed tomography and magnetic resonance imaging (MRI) are useful in excluding alternate sources for hyperammonaemia such as porto-systemic shunting, reversible encephalopathy syndrome, diffuse hypoxic ischaemic injury and seizure activity.[3] Neuroimaging can range from normal to diffuse cerebral oedema in severe hyperammonaemia. Diffusion restrictions affecting the insular cortex and gyri are commonly seen on MRI, the reason for which is unknown.[3,106] These changes are often reversible but can also lead to atrophy.[106]

CONCLUSION

Consideration of hyperammonaemia presents a challenge to the physician in the acute setting where diagnoses are broad and clinical presentations are largely non-specific. Incorrect or poor management of an acute crisis carries significant morbidity and mortality. The rarity of these diseases underlying non-cirrhotic hyperammonaemia results in a paucity of evidence and thus a lack of robust recommendations surrounding evaluation and management. This review presents all the available evidence to assist chemical pathologists and clinicians in the acute setting to rapidly establish the cause of hyperammonaemia, as these patients usually require specific therapies.

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