What adult neurologists need to understand about ammonia

Meijer RI[1,2]*, Vivekananda U[3]*, Balestrini S[3], Walker MC[3], Lachmann RH[1], Häberle J[4], Murphy E[1]

[1]Charles Dent Metabolic Unit, The National Hospital for Neurology and Neurosurgery, London, United Kingdom

[2]Department of Internal Medicine, Amsterdam University Medical Centers, Location VU University Medical Center, Amsterdam, The Netherlands

[3]Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, London, United Kingdom

[4]University Children's Hospital Zurich and Children's Research Centre, Zurich, Switzerland

* Both authors contributed equally.

Address for correspondence

Dr Elaine Murphy

Consultant Adult Inherited Metabolic Disease

Charles Dent Metabolic Unit, Internal Mailbox 92

National Hospital for Neurology and Neurosurgery

Queen Square

London WC1N 3BG

Tel: +44 203 448 4778

Email: elaine.murphy8@nhs.net

Key words

Ammonia; hyperammonemia; encephalopathy; urea cycle; anti-epileptic; hemodialysis

Key points

1. The symptoms and signs of hyperammonemia include lethargy, nausea, anorexia, encephalopathy, hyperventilation or hypoventilation, seizures, cerebral oedema and coma.
2. The most common cause of hyperammonemia in adult practice is liver disease. In neurologic practice, hyperammonemia secondary to anti-epileptic medication is common.

3. Inherited disorders of metabolism are a rare (treatable) cause of first presentation of hyperammonemia in adults. Of these, the urea cycle defect ornithine transcarbamylase deficiency is the most frequently encountered.
4. Emergency management of acute severe hyperammonemia is based on 3 complementary principles: prevention / reversal of the catabolic state, physical removal of ammonia by renal replacement therapy (hemodialysis / hemo(dia)filtration) and pharmacologic scavenging of excess nitrogen.

Word count = 3521 (excluding table)

Tables = 1

Figures = 1

Abstract

Hyperammonemia is often encountered in acute neurology, and can be the cause of acute or chronic neurological symptoms. Patients with hyperammonemia may present with seizures or encephalopathy, or may be entirely asymptomatic. The underlying causes are diverse but often straightforward to diagnose, although sometimes require specialist investigations. Hemodialysis or hemo(dia)filtration is the first-line treatment for acute severe hyperammonemia (of any cause) in an adult. Here we discuss our approach to adult patients with hyperammonemia identified by a neurologist.

Introduction

Hyperammonemia is frequently encountered in adult neurologic practice, usually in the context of encephalopathy, seizures or (more rarely) coma.

With a typical dietary intake of approximately 100 g protein / day, adults produce around 1000 mmol of ammonia daily [1]. Ammonia is released from the metabolism of protein in food and body tissues. It has an important role in metabolism as a source of nitrogen, in amino acid synthesis and in acid-base balance. However, the majority of ammonia produced carries waste nitrogen, and, as it is neurotoxic, must be disposed of efficiently. Most ammonia is excreted in urine as urea, with a smaller amount as ammonium ions.

Figure 1 summarises the metabolism of ammonia. Ammonia produced in peripheral tissues is incorporated into glutamine, which is non-toxic at normal concentrations. Glutamine is transported to the intestine, where ammonia is released again by hydrolysis. Ammonia is also produced *de novo* in the gut by the action of bacteria and mucosal enzymes on dietary protein. After uptake by the colon, ammonia is transported to the liver in the portal blood where it enters the periportal hepatocytes and is converted to urea by the urea cycle. Urea is subsequently filtered and excreted in urine.

The complete enzyme system of the urea cycle is only expressed in the liver which is the only organ which can generate urea from ammonia. This is why hyperammonemia is a common finding in liver failure. Hyperammonemia can broadly be caused by either increased production or reduced elimination, and making that distinction has implications for its management. Increased production is generally the result of acquired conditions, whereas reduced elimination can be the result of either acquired or inherited conditions (see table).

Pathogenesis of neurological symptoms

Hyperammonemic encephalopathy was thought to be due to ammonia crossing the blood brain barrier and being taken up by astrocytes which then detoxified it to glutamine, altering astrocytic osmotic pressure and causing astrocyte swelling and ultimately increased intracerebral pressure. However, more recent data suggest that astrocyte swelling or brain

oedema may not be so important in the acute phase, with a direct effect of ammonia on glial and neuronal function playing a greater role. It has been proposed that excessive ammonia in the brain impairs inhibitory neurotransmission and decreases astrocyte potassium buffering, thus lowering the seizure threshold [2].

Signs and symptoms

There is often a poor correlation between the symptoms of hyperammonemia and the absolute plasma ammonia concentration. An acute rise in plasma ammonia concentration will often precipitate symptoms, whereas patients with a chronically elevated concentration may appear asymptomatic.

Initial symptoms of acute hyperammonemia may be mistaken for alcohol / drug intoxication, viral encephalitis or psychiatric disease. Features include altered behaviour (being 'not quite right'), irritability and aggression (be careful not to ascribe post-partum hyperammonemia to post-partum psychosis or depression). Other sub-acute symptoms include lethargy, headache, nausea, vomiting, disorientation, delusions, and somnolence. Neurological signs such as ataxia and hemiparesis have been described (although in our experience these are rare in patients presenting in adulthood). Frank hyperammonemic encephalopathy is clinically characterized by an acute or subacute decreasing level of consciousness that progresses from lethargy to drowsiness and coma. Seizures, or an increase in the frequency of seizures can also occur.

History

What is the precipitant for hyperammonemia?

The table lists the potential triggers of hyperammonemia in an adult, of these some of the most commonly encountered include:

- Liver disease (estimated to account for up to 90% of cases of hyperammonemia in adulthood). Cirrhosis and end-stage liver disease are well-recognized causes, but other causes such as portal vein thrombosis, or a portosytemic shunt (secondary to trauma, surgery, or congenital vascular anomalies) should also be considered. Liver disease will not be discussed further in this article.
- Introduction of a new medication or an increased dose of medication (e.g. anti-epileptics).
- Infection or fever i.e. catabolism, particularly in individuals with a urea cycle defect.
- Fasting e.g. deliberately for weight loss, or around the time of gastrointestinal surgery.
- Severe gastrointestinal or internal bleeding (i.e. the equivalent of a high protein load for metabolism).
- Catabolism and involution of the uterus in the post-partum period (a well-recognised cause of hyperammonemia in women with a urea cycle defect).

Does the history suggest that this is acute or chronic?

Chronic

- Lifelong protein aversion (patient may be shorter or lighter than other family members; self-selected vegetarian diet)
- Chronic intermittent headaches (may be worsened by higher protein meals)
- Abdominal pain and nausea after higher protein meals
- Intermittent (self-resolving) episodes of confusion, irritability, aggression

Acute

- Rapid onset of severe symptoms – encephalopathy, seizures, impaired consciousness (NB. needs immediate emergency management).

Taking blood for ammonia measurement

In an urgent situation, where significant hyperammonemia is suspected

Venous or arterial blood should be collected without a tourniquet, and without muscle contraction. Blood should preferably be collected in a pre-chilled container. After drawing, the container should be placed on ice-water and transported to the biochemistry laboratory immediately. Avoid freezing the sample as this increases the risk of haemolysis. Once there, it should be processed without delay. A delay in cooling or processing may falsely increase the ammonia concentration due to the production of ammonia by erythrocytes.

In practice, as long as a sample is taken without haemolysis and delivered to the laboratory within 15 minutes of collection for processing then it is suitable for analysis. Laboratory accreditation guidelines (http://www.metbio.net) in the UK state that laboratories should be able to provide an ammonia concentration within 1 hour of an urgent request.

For monitoring, or a non-urgent situation

Although there may be a case for fasting a patient before ammonia is measured (in order to obtain more consistent results), in routine practice, this is rarely done, although pre-prandial samples (ie. ideally 3 to 4 hours after the last meal) are generally preferred. Ammonia concentrations will be higher after a protein-containing meal, and protein-loading can be used, with caution, to reveal transient hyperammonemia. In the ideal situation, a patient should preferably not smoke in the hours preceding blood withdrawal, as smoking increases the ammonia content in the blood.

What are the initial investigative tests to request?

In an acute / subacute situation with suspected hyperammonemia the following tests should be requested:

- Ammonia (reference ranges vary slightly between laboratories, but in an adult is usually < 40 umol/L)
- Full blood count
- Renal and liver profiles
- Urea (may be inappropriately low compared to other markers of renal function / dehydration in urea cycle defects)
- Coagulation screen
- CRP and septic screen, blood cultures etc.
- Plasma glucose (hypoglycaemia may occur in e.g. fatty acid oxidation disorders, hyperinsulinism or liver failure)
- Lactate
- Creatine kinase
- Blood gas - calculate the anion gap (ammonia is a respiratory stimulant therefore hyperammonemia causes a respiratory alkalosis. The presence of a metabolic acidosis may suggest an organic acidemia or a fatty acid oxidation defect).
- Urine ketones
- Drug screen (but beware of attributing all symptoms to alcohol or drugs)

If the cause of hyperammonemia is unknown, then also take the following diagnostic samples (store appropriately in your laboratory for later analysis if these specialist investigations are not available locally). If possible collect samples before specific treatment is instituted, but do not postpone treatment to collect samples in an emergency with acute severe hyperammonemia.

- Plasma amino acid profile (in the pre-prandial state if possible; but take at any point if it is an emergency)
- Acylcarnitine profile (to investigate for a fatty acid oxidation disorder)
- Urine organic acid profile including orotic acid (a true first presentation of an organic acidemia in adulthood would be extremely rare, but milder cases may not have been diagnosed in childhood, so should be considered in the differential)
- DNA (for later genetic analysis if indicated)

If an inherited disorder of urea cycle metabolism is suspected the amino acid profile will be key in suggesting a diagnosis. Specific enzyme activities can be measured (in red blood cells, liver or fibroblasts, depending on the enzyme to be assayed) but genetic testing (hyperammonemia panels or exome sequencing) is now the method of choice for confirming suspected inherited conditions, with enzyme testing reserved for unclear situations or research.

The EEG usually shows rhythmical theta and delta activity in keeping with encephalopathy. In more severe cases, triphasic waves may be present. During acute hyperammonemia, MRI imaging may be normal or may include symmetric involvement of the cingulate gyrus and

insular cortex with more variable and asymmetric additional cortical involvement. This is often most evident with diffusion-weighted imaging, showing areas of restricted diffusion. Treatment should not be delayed if the MRI brain is normal. Treatment decisions should be made on the degree of hyperammonemia and clinical presentation (see below).

If a chronic disorder is suspected (e.g. in an individual with longstanding episodic symptoms, developmental delay or learning difficulties) and the patient reports a restricted diet then also consider other investigations such as vitamin B12 and D concentrations, iron studies, a bone density scan etc. as indicated.

How to interpret the amino acid profile in the context of hyperammonemia

Interpreting an amino acid profile, with its 20 or more different components, may initially seem daunting, particularly if little is known about the context in which the sample has been taken (e.g. pre-or post-prandial, pre-or post-hemodialysis). Try to get into the habit of carefully labelling amino acid samples with some contextual information – to make later interpretation more straightforward. With a stepwise and logical approach an amino acid profile can be very useful, particularly in suggesting a diagnosis of an inherited disorder of metabolism.

One suggested approach is as below:

- Glutamine and alanine: are they elevated? This suggests that increased ammonia is being transported in the blood as glutamine and alanine.
- Arginine and citrulline: are they low? This might suggest the urea cycle defect ornithine transcarbamylase deficiency, the most common of the urea cycle disorders to present in adulthood.
- Arginine: is it very elevated i.e. >300 µmol/L? In the context of hyperammonemia this would suggest the urea cycle defect arginase deficiency.
- Citrulline: is it very elevated? This might suggest citrulinaemia type I, due to argininosuccinate synthetase deficiency (argininosuccinic acid (ASA) will be absent) or arginosuccinic aciduria, due to argininosuccinate lyase deficiency (ASA will be elevated).

In addition:

- Essential amino acids e.g. isoleucine, leucine, phenylalanine and valine: are they low? This might suggest that the patient has been avoiding foods of higher protein content.
- Total homocysteine: is it elevated? This might suggest that the patient avoids dietary animal protein i.e. may be vitamin B12 deficient.

What are the immediate treatment steps to take for acute hyperammonemia?

- Stop dietary protein intake (for 24 hours initially, then review with a specialist metabolic dietitian. If protein is withheld for a prolonged period then further catabolism (in an attempt to supply essential amino acids) will occur and this may prolong hyperammonemia)
- Ensure sufficient calories to prevent further catabolism (from a non-protein source e.g. 10% dextrose intravenous infusion initially and monitor / replace electrolytes as required)
- Remove / reduce the precipitant (medication etc)
- Treat intercurrent infection

At what ammonia concentration should more specific treatment be considered?

This is a clinical decision depending on factors such as patient symptoms, the duration of symptoms at presentation, the underlying precipitant and the rapidity of development of hyperammonemia. There is no exact ammonia concentration at which a specific treatment is indicated and clinical judgement should be used, but, broadly speaking, for adults:

- with a plasma ammonia >200 µmol/L and evolving symptoms - monitor in HDU / ITU and consider immediate hemodialysis or hemo(dia)fltration.
- with a plasma ammonia < 120 µmol/L and without encephalopathy - monitor and treat with general measures. Consider oral / intravenous nitrogen scavenger medications. Escalate treatment if the ammonia concentration increases or symptoms worsen.
- with a plasma ammonia 120-200 µmol/L - assess carefully very regularly. Start intravenous ammonia scavenger medications, but have a very low threshold to switch to hemodialysis or hemo(dia)filtration. These procedures are well-tolerated in an adult and can be started in most adult ITU settings.

In general, we do not recommend transfer of an adult with acute hyperammonemia to a specialist centre – as in our experience this only results in delays to starting treatment and patients can deteriorate quickly during transfer. Once the acute hyperammonemia is treated, and the patient is stable, then transfer for specialist dietary input and optimisation of medications can be discussed.

In our experience, an ammonia concentration of >500 µmol/L in an adult patient generally correlates with a poor prognosis. However, a very high ammonia concentration is not an absolute criterion and should be evaluated together with the clinical findings and the duration of hyperammonemia. Patients with a normal outcome despite very high initial ammonia have been reported.

Specific treatment of acute severe hyperammonemia

The first-line treatment for an adult with acute symptomatic hyperammonemia (of any cause) is hemodialysis or hemo(dia)filtration [3]. This is the quickest, most efficient way to reduce ammonia concentration and can be arranged in a general or district hospital ITU when specialist medications (see below) may not be available.

Intravenous nitrogen scavengers (sodium benzoate and sodium phenylbutyrate) can be used to avoid the need for dialysis in some patients (these can be couriered from the specialist metabolic pharmacies to any hospital in the UK and many paediatric hospitals will also stock these medications routinely). Details of these drugs and their use in the management of hyperammonemia are available from the British Inherited Metabolic Disease Group (BIMDG) (http://www.bimdg.org.uk/site/formularies.asp, http://www.bimdg.org.uk/site/guidelines.asp).

Early treatment is essential to prevent irreversible cerebral oedema. Patients presenting to the emergency department with hyperammonemia should therefore always be triaged with high priority, treated seriously, and the threshold for admission to an HDU/ITU setting should be low. Patients with known urea cycle defects should arrive with their own printed emergency regimen to be followed if they are unwell.

Supportive treatment with analgesia, antipyretics, antibiotics or anti-emetics as needed is also important. For patients known or suspected to have an inherited disorder of metabolism, early contact with a specialist adult metabolic centre and their associated dietitians should be made to guide treatment.

Anti-epileptic medication and hyperammonemia

Hyperammonemia is frequently reported in patients taking anti-epileptic medication, notably sodium valproate and topiramate. The reported prevalence of hyperammonemia in patients receiving valproate therapy is variable, ranging from 2-80% [4]. In a review of 183 studies between 1980 and 2005, serum ammonia increased from a baseline of 29+/-8 µmol/L to 54+/-16 µmol/L after valproate therapy alone. Although the majority of patients are asymptomatic, symptomatic hyperammonemic encephalopathy is described and the risk of hyperammonemia appears to increase in a dose-dependent manner. This effect is more marked in patients who also take hepatic enzyme inducers such as phenytoin, phenobarbital, carbamazepine, or combinations of these drugs.

This is consistent with our own experience; in a review of 77 patients with epilepsy, higher doses of valproate and polytherapy with multiple anti-epileptic medications were risk factors for hyperammonemia. Treatment adjustment in symptomatic patients with hyperammonemia led to an improvement of clinical symptoms (personal communication Dr Angeliki Vakrinou, National Hospital for Neurology and Neurosurgery, Queen Square).

Several mechanisms may contribute to valproate-induced hyperammonemia. It is metabolised to valproyl-CoA in the mitochondria, which inhibits N-acetylglutamate synthase, thereby limiting detoxification of ammonia to carbamoyl phosphate and also resulting in secondary carnitine deficiency [5]. Valproate also increases renal ammonia production by enhancing glutamine uptake in the renal mitochondria. Glutamine (and water) are subsequently converted to glutamate and ammonia in the renal tubules.

In the event of encephalopathy, worsening seizures, behavioural change or increased gastrointestinal side-effects (in particular nausea and vomiting) in patients taking valproate, we would recommend measurement of ammonia. There is very limited evidence as to the most appropriate treatment but the following can be considered:

- Discontinue or reduce the dose of valproate if at all possible.
- Ask the patient to complete a diet diary to ensure that protein intake is not excessive.
- Consider carnitine supplementation (eg. 50 mg/kg/day) if the carnitine concentration is low.
- Add oral nitrogen scavenger medication (sodium benzoate, sodium phenylbutyrate, glycerol phenylbutyrate) to the patient's treatment.

Hyperammonemia as a result of topiramate therapy has mostly been reported when taken in combination with valproate, and in rare circumstances leads to encephalopathy. Topirimate is thought to affect bicarbonate availability in the liver and glutamine synthesis in the brain, resulting in hyperammonemia.

Other drugs that more rarely cause hyperammonemia are listed in the table.

Another important source of ammonia is deamination of adenosine monophosphate in skeletal muscle, as can happen when it becomes damaged, e.g. by seizures. Elevated plasma ammonia associated with seizures appears transient in nature, with levels returning to normal within 8 hours, and is not predictive of clinical outcome.

Inherited metabolic disorders

Primary urea cycle defects, resulting from an inherited defect in one of the six enzymes or two transporters of the urea cycle, although rare, are important treatable causes of hyperammonemia (figure 1) [3]. Ornithine transcarbamylase deficiency is by far the most common urea cycle defect (>60% of all cases). It is an X-linked disorder and in male hemizygotes is generally fatal in the infantile period, although late (adolescent / adult) presentation is known to be associated with specific genotypes. In female heterozygotes, however, the situation is different and these patients can present at any age often with subacute symptoms. Initial presentation in the post-partum period is well recognised and is

thought to relate to changes in maternal metabolism and the large protein load provided by involution of the uterus.

Other inherited disorders which can also present with hyperammonemia, such as the fatty acid oxidation disorders or the organic acidemias, typically present in childhood and only very rarely come to light for the first time in adulthood. However, in a known adult patient with one of these conditions, the presence of hyperammonemia generally indicates a severe metabolic decompensation and prompt treatment with monitoring in a HDU or ITU setting is likely to be required.

Chronic management of patients with inherited metabolic diseases should be led by a specialist centre and may include a prescribed low protein diet, oral nitrogen scavenger medication, and other medications that support the endogenous ammonia-detoxifying metabolic pathways, such as L-arginine, carglumic acid (a synthetic analogue of N-acetylglutamate which acts as an allosteric activator of the urea cycle) and L-citrulline.

Medications that are commonly used in the management of hyperammonemia secondary to hepatic encephalopathy, such as lactulose and rifaximin, are minimally effective in the management of inherited urea cycle disorders and are not generally recommended, particularly not in the acute situation.

Conclusion

Hyperammonemia is a frequent finding in patients with neurological disorders such as epilepsy and encephalopathy. A systematic and logical approach to diagnosis will usually reveal an underlying cause. Acute severe hyperammonemia is a medical emergency, treatable by hemodialysis. The treatment of chronic hyperammonemia depends on the underlying cause, with the primary goal of identifying and removing / reducing any precipitant(s).

Figures and table

Figure 1: Mechanism of ammonia production in the body.

Metabolism of food and body tissues produces ammonia ($NH4^+$) as a by-product. Ammonia is transported to the liver, converted into non-toxic urea in the urea cycle, and subsequently excreted by the kidneys. Urea production increases linearly with increasing protein intake. On a high-normal protein intake of around 100 g / day, adults produce around 1000 mmol of ammonia daily, whilst maintaining a plasma concentration of less than 40 µmol/L.

There are two primary carriers of amino groups in the blood, glutamine and alanine. Muscle tissues catabolize amino acids for a source of energy. In the muscle, excess ammonia is transferred to pyruvate to form alanine by alanine aminotransferase. Alanine is released into the blood stream. The liver absorbs the alanine, and deaminates it to reform pyruvate. Other tissues such as brain tissue take excess ammonia, react it with glutamate to form glutamine by the enzymatic action of glutamine synthetase. Glutamine is then released into the blood stream and also absorbed by the liver. In the liver, the enzyme glutaminase hydrolyzes the glutamine into glutamate. Glutamate then enters the urea cycle.

The liver is the only organ that has the full complement of urea cycle enzymes. The first three enzymes (N-acetylglutamate synthase, NAGS; carbamoyl phosphate synthetase I, CPS1; ornithine transcarbamylase, OTC) are intramitochondrial. The second three are cytosolic (argininosuccinic acid synthetase; arginosuccinic acid lyase; arginase). Two carriers, supplying ornithine and aspartate (labelled [A] and [B] respectively in the figure), are also essential for normal functioning of the cycle. With every turn of the urea cycle, two atoms of nitrogen are converted to urea.

When carbamoyl phosphate accumulates as the result of a urea cycle defect, it diffuses out of the mitochondria and enters the pathway for pyrimidine synthesis. As a result, orotic acid is produced, which is then excreted in the urine, and can be detected in a urine organic acid profile.

Table: Causes and precipitants of hyperammonemia.

INCREASED AMMONIA PRODUCTION	REDUCED AMMONIA ELIMINATION
Increased protein intake	***Medications***
Gastrointestinal haemorrhage	Valproate
Excess dietary protein intake	Topiramate
(including enteral or parenteral feeding)	Carbamazepine
	5-Flurouracil
Increased catabolism	Rifabutin
Seizures	Acetazolamide
Corticosteroid use	
Starvation	
Malignancy (hepatic carcinoma, multiple myeloma,	***Liver disease***
leukaemia, treatment with asparaginase)	Cirrhosis
Excessive exercise	Acute liver failure
Trauma or burns	Reduced liver perfusion
	Hepatic or portal vein thrombosis
Infection	Portosystemic shunting
Enteral bacterial overgrowth	
Urinary tract infection with urea splitting bacteria	
(Proteus, Pseudomonas, Klebsiella, coagulase	
negative Staphylococcus, and Mycoplasma)	***Inherited metabolic disease***
	Urea cycle defects
Renal ammonia production	Ornithine transcarbamylase (OTC) deficiency
Hypokalemia	Carbamyl phosphate synthetase 1 (CPS) deficiency
Alkalosis	Argininosuccinate synthetase deficiency
Reduced perfusion	Argininosuccinate lyase deficiency
	N-acetyl glutamate synthase (NAGS) deficiency
Others	Arginase deficiency
Salicylate intoxication	Hyperornithinemia-hyperammonemia-homocitrullinuria
Shock	(HHH) syndrome
	Citrin deficiency
Sampling / laboratory issues	
Poor specimen quality / haemolysis	**Fatty acid oxidation disorders (examples)**
Difficult venepuncture	Primary carnitine deficiency
Delayed analysis of the sample	Carnitine palmitoyl transferase 1 (CPT1) deficiency
	Organic acidemias (examples)
	Methylmalonic acidemia
	Propionic acidemia
	Others
	Lysinuric protein intolerance
	Hyperinsulinism-hyperammonemia (HI-HA) syndrome
	Δ1-pyrroline-5-carboxylate synthetase deficiency

References

1. Walker, V., *Ammonia metabolism and hyperammonemic disorders.* Adv Clin Chem, 2014. **67**: p. 73-150.
2. Rangroo Thrane, V., et al., *Ammonia triggers neuronal disinhibition and seizures by impairing astrocyte potassium buffering.* Nat Med, 2013. **19**(12): p. 1643-8.
3. Haberle, J., et al., *Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision.* J Inherit Metab Dis, 2019. **42**(6): p. 1192-1230.
4. Tseng, Y.L., et al., *Risk factors of hyperammonemia in patients with epilepsy under valproic acid therapy.* Medicine (Baltimore), 2014. **93**(11): p. e66.
5. Aires, C.C., et al., *New insights on the mechanisms of valproate-induced hyperammonemia: inhibition of hepatic N-acetylglutamate synthase activity by valproyl-CoA.* J Hepatol, 2011. **55**(2): p. 426-34.