Eur J Pediatr (2011) 170:21 34
DOI 10.1007/s00431 010 1369 2

REVIEW

Clinical practice

The management of hyperammonemia

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Received: 20 October 2010 / Revised: 22 November 2010 / Accepted: 24 November 2010 / Published online: 17 December 2010
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Abstract Hyperammonemia is a life-threatening condition which can affect patients at any age. Elevations of ammonia in plasma indicate its increased production and/or decreased detoxification. The hepatic urea cycle is the main pathway to detoxify ammonia; it can be defective due to an inherited enzyme deficiency or secondary to accumulated toxic metabolites or substrate depletion. Clinical signs and symptoms in hyperammonemia are unspecific but they are mostly neurological. Thus, in any unexplained change in consciousness or in any unexplained encephalopathy, hyperammonemia must be excluded as fast as possible. Any delay in recognition and start of treatment of hyperammonemia may have deleterious consequences for the patient. Treatment largely depends on the underlying cause but is, at least in pediatric patients, mainly aimed at establishing anabolism to avoid endogenous protein breakdown and amino acid imbalances. In addition, pharmacological treatment options exist to improve urea cycle function or to remove nitrogen, but their use depend on the underlying disorder. To improve the prognosis of acute hyperammonemia, an increased awareness of this condition is probably more needed than anything else. Likewise, the immediate start of appropriate therapy is of utmost importance. This review focuses on a better understanding of factors leading to ammonia elevations and on practical aspects related to diagnosis and treatment in order to improve clinical management of hyperammonemia.

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Keywords Ammonia · Glutamine · Urea cycle · Nitrogen metabolism · Awareness · Neurotoxicity · Cerebral edema

Introduction

Hyperammonemic disorders not due to general liver failure are rare and the symptoms non-specific. The clinical presentation varies depending on age of the patient and on type and severity of the underlying disorder. In all age groups, loss of appetite and then vomiting are early and reversible findings if treated. In newborns, first symptoms are poor feeding, vomiting, seizures, unstable body temperature, respiratory distress or poor peripheral blood circulation leading to an initial suspicion of intracranial bleeding, septicemia or meningitis; in infants, vomiting may evoke pyloric stenosis, cow milk intolerance or infectious enteritis; in children, adolescents and adults, vomiting, ataxia, confusion, disorientation, hallucinations or abnormal behavior point to central nervous system or psychiatric disorders. In all age groups, the change of consciousness should shift the search to intoxications, encephalitis or metabolic disorders. Since more common disorders are considered first, valuable time is often lost when hyperammonemia has already reached levels above 400–500 μmol/L thus increasing the risk of irreversible brain damage, of neurodevelopmental retardation or even death.

The first goal of this review is to stimulate the reader to consider the rare metabolic disorders in presence of non-specific symptoms in order to rule out hyperammonemia and—if present—to prevent irreversible damage to the brain by timely action. The second goal is to outline the principles of the available treatments and necessary controls in order to empower the pediatrician to follow and guide

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the patient when the disorder has been diagnosed. An increased awareness of all medical professionals towards the possibility of hyperammonemia is needed for an improved prognosis of affected patients.

Background

Physiology

About 90% of nitrogen-containing compounds are normally excreted as urea. They originate from the obligate oxidation of amino acids and from excess waste nitrogen, mainly from amino acids not used for protein neo-synthesis, from cell turnover of hydrolyzed body protein and from protein intake. The bulk of protein mass is in the skeletal and visceral musculature. The rate of protein breakdown is relatively constant while the synthesis is regulated e.g. by hormones, cytokines and available substrates. The capacity of urea formation adapts normally within a few days to changes of the amount of protein intake.

Ammonia (NH_3) is a constituent of all human body fluids and at neutral pH present mostly (>98%) in its ionized form, ammonium (NH_4^+) [8]. This is physiologically advantageous because ammonium, in comparison to ammonia, barely permeates cell membranes. Mainly for convention, "ammonia" is used in this review although "ammonium" would be the correct biochemical term. The concentration of ammonia in human plasma is micromolar and varies in venous, arterial or capillary blood as well as depending on the time and mode of sampling (see below). Tissue ammonia concentrations are higher and ammonia is trapped as ammonium in compartments with lower pH such as in lysosomes and renal tubules [3]. Plasma ammonia concentrations depend on the age of the patient and assay method used but it should be noted that well-defined reference limits for ammonia do not exist (limits for use in clinical practice are depicted in Table 1 [18]).

Hyperammonemia indicates an elevation of ammonia in blood and tissues by its increased production and/or decreased detoxification and is a strong indicator of abnormal nitrogen homeostasis. Since in clinical practice ammonia can be determined very fast but also because of the associated neurotoxicity, ammonia belongs to the core parameters of metabolic medicine together with blood gases, glucose, lactate and ketone bodies. However, the clinical condition of a patient should guide the management rather than solely ammonia concentrations because they can be fluctuating and may not entirely correlate with already impaired brain function.

In mammals, skeletal muscle and intestinal mucosa are mainly responsible for ammonia production (Fig. 1a). Many of the reactions of amino acid metabolism take place in skeletal muscle, where protein is broken down and where single amino acids are transaminated for new protein synthesis or to form glutamine from glutamate and/or alanine from pyruvate [28]. Glutamine is not only the most abundant amino acid in the human organism, the temporary storage form of waste nitrogen and the main transport form of amino groups between organs but also a major source of ammonia if deaminated by glutaminase [48]. Also in skeletal muscle, deamination of adenosine monophosphate, particularly during physical exercise, results in ammonia production. In intestinal mucosa, ammonia is produced after uptake of amino acids as a result of glutamine deamination. In colon and bladder, microorganisms expressing enzymes enabling protein and urea degradation, respectively, can lead to hyperammonemia [40, 41, 66, 67]. About 25% of endogenous ammonia is derived from intestinal production [46, 63].

For the final transformation of glutamine/glutamate to ammonia and for detoxification of the portal ammonia and export of ammonia, the liver and to a certain extent the kidney play the central role. In liver, the urea cycle is located in periportal hepatocytes and provides a high capacity for detoxification of the vast amount of surplus nitrogen while glutamine synthetase, expressed only in perivenous hepatocytes, serves as back-up system with high affinity (but low capacity) to ammonia (Fig. 1b) [36]. Accordingly, hyperammonemia can occur in many acquired and inherited hepatic disorders. In kidney, ammonia is formed from glutamine deamination. However, renal ammonia production mainly contributes to buffering H^+ ions while excretion of ammonia in urine plays only a minor role in overall ammonia detoxification (Fig. 1a and b show the key players of ammonia production and detoxification).

Table 1 Plasma ammonia concentrations depending on age of patients (adapted from [18])

	μmol/l	μg/dl
Newborns (arterial cord blood)	50 159	85 271
Infants and children	24 48	41 82
Adults (female)	11 48	19 82
Adults (male)	15 55	26 94

Conversion μg/dl×0.5872=μmol/l. The levels given are decision limits which should be interpreted together with the clinical situation

Practical points

- ➢ Ammonia is neurotoxic itself and indicates increased ammonia production or decreased ammonia detoxification
- ➢ Ammonia determination is crucial for many metabolic disorders
- ➢ The neurological condition of the patient should guide the clinical management rather than ammonia levels alone

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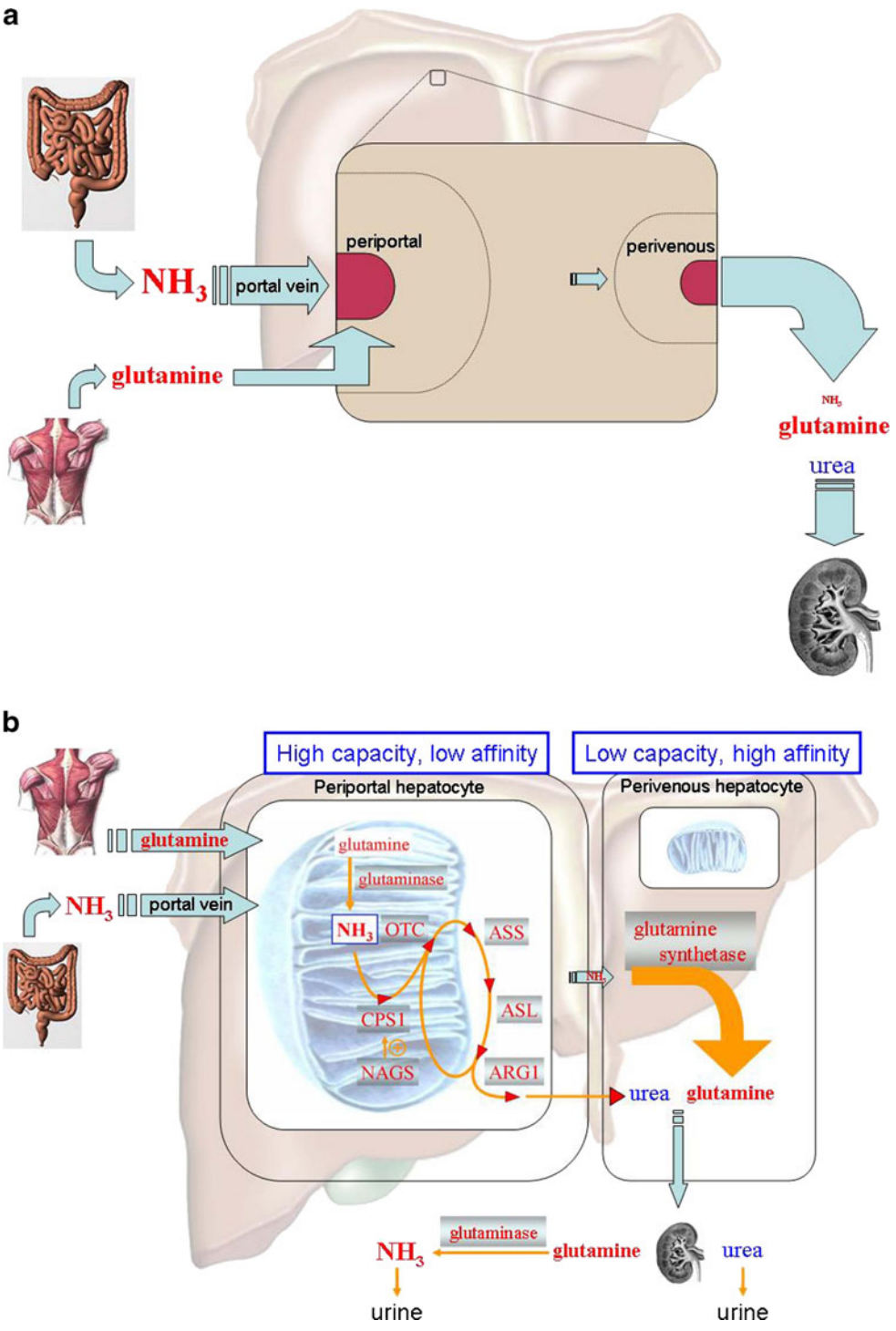

Fig. 1 **a**, **b**. Illustration of the key players of ammonia pro duction and detoxification. **a** Simplified graph showing the interplay of intestine and skele tal muscle (organs that produce ammonia and glutamine) with liver and kidney (organs that detoxify ammonia). Ammonia is detoxified in liver while gluta mine is not. **b** This simplified graph focuses on periportal and perivenous hepatocytes as the two ammonia detoxifying com partments in liver. Ammonia is metabolized with high capacity but low affinity in the urea cycle which is solely expressed in periportal hepatocytes. As back up, ammonia is detoxified by the action of glutamine syn thetase that is solely expressed in perivenous hepatocytes and has a low capacity but high affinity towards ammonia. Urea and glutamine re enter the cir culation to be excreted in urine or further metabolized in the kidney, respectively. Urea cycle enzymes abbreviated: *NAGS N* acetylglutamate synthase, *CPS1* carbamoylphosphate synthetase 1, *OTC* ornithine transcarbamy lase, *ASS* argininosuccinate syn thetase, *ASL* argininosuccinate lyase, *ARG1* arginase 1

Neurotoxicity of ammonia

The brain is the main organ affected by hyperammonemia [21]. Ammonia enters the brain mainly by diffusion, but it is to a lesser extent also produced by brain metabolism [47]. A number of reversible and irreversible metabolic and neurotransmitter disturbances and ensuing morphologic changes add up to severe brain toxicity but the exact pathogenic mechanisms still need to be unraveled [4, 15, 29, 31]. Depending on age as well as duration and level of hyperammonemia severe cerebral edema, brain stem herni- ation and death can result. In acute hyperammonemia, astrocytes are swollen as observed by microscopy. One important factor in this pathology is the osmotic effect of newly synthesized brain glutamine on astrocytes which is taken up together with water [13, 69] but many other

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mechanisms contributing to brain toxicity of ammonia have been suggested and the reader is referred to recent reviews [4, 10, 11, 14, 44, 62].

Metabolic crisis

Metabolic crises occur whenever the load of waste nitrogen exceeds the detoxification capacity. In the periportal liver (and to a lesser extent in the intestinal mucosa), the main part of ammonia from the gut is handled by urea synthesis [36]. All enzymes and membrane transporters needed are expressed in these cell systems [17, 48, 51]. In all other organs and cell systems including perivenous hepatocytes, amino groups and ammonia are detoxified by glutamine formation [37].

If the capacity for detoxification of ammonia is insufficient a vicious cycle can lead to crises. This occurs when the increasing systemic ammonia leads to loss of appetite and vomiting. Rapid intervention is needed to avoid a further increase of ammonia, i.e. when protein synthesis is reduced and catabolism prevails like during postpartum physiologic weight loss in neonates, infections (even minor ones) or increase of nutritional protein supply beyond the actual needs.

Therapeutic measures are initially non-specific in order to reduce hyperammonemia below 400–500 μmol/L or optimally prevent its rise to such levels; a rapid diagnosis should be reached to allow the application of more efficient measures [6, 43]. Otherwise, the risk of irreversible damage to the brain is high.

Biochemical basis of primary hyperammonemia

In the mammalian organism, the major part of ammonia is detoxified by the urea cycle (Figs. 1a, b and 2). This cycle is fully expressed only in liver and intestinal mucosa and comprises six enzymatic steps of which three are intramitochondrial and three cytosolic [36]. The urea cycle has a second role—the synthesis of arginine—which is important for the treatment of hyperammonemia [12].

A defect in one of the six urea cycle enzymes and two membrane transporters results in so called primary hyperammonemia, while metabolic defects outside the urea cycle as well as side effects of drugs can lead to secondary hyperammonemia. This classification is by no means purely academic but is part of any differential diagnosis of unexplained hyperammonemia (Table 3).

The single most important of the urea cycle disorders (UCDs) is ornithine transcarbamylase (OTC) deficiency because it is the most common one and the only X-linked [57]. While male patients are often affected by severe neonatal metabolic decompensation, females with OTC

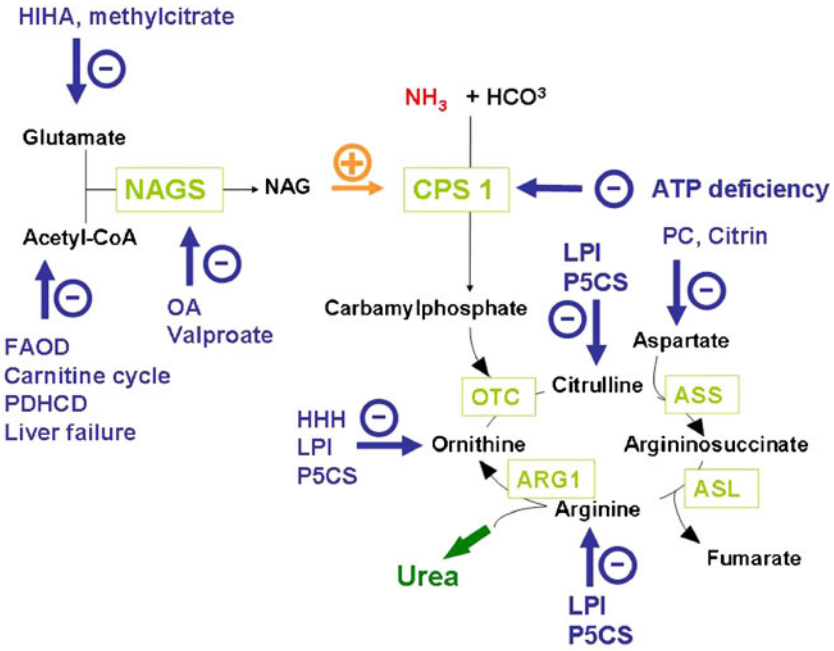

Fig. 2 Influence of metabolic disorders on function of urea cycle leading to secondary hyperammonemia. Figure showing sites of action of various compounds on urea cycle function by either leading to inhibition of enzymes (NAGS or CPS1) or to a decrease in intermediate substrates (both negative actions are depicted as ⊖). *HIHA* hyperinsulinism hyperammonemia syndrome, *FAOD* fatty acid oxidation defects, *PDHCD* pyruvate dehydrogenase complex disorders, *OA* organic acidemias, *HHH* hyperornithinemia hyperammonemia homocitrullinuria syndrome, *PC* pyruvate carboxylase defect, *Citrin* Citrullinemia type 2, *LPI* lysinuric protein intolerance, *P5CS* pyrroline 5 carboxylate synthetase defect. The site of action of valproate has also been added. ⊕ depicts the stimulatory effect of NAG on CPS1. Figure adapted from [53]

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deficiency can present with a broad clinical picture [57, 59]. Depending on random X-inactivation, the resulting OTC phenotype is a continuum and affected females may remain asymptomatic but may also resemble hemizygous males [50]. All other UCDs are autosomal recessively inherited.

Biochemical basis of secondary hyperammonemia

Many inborn errors of metabolism result in accumulation of toxic products which can lead to inhibition of other metabolic pathways (Fig. 2). This is also the case for the urea cycle which can loose its ammonia detoxifying capacity because accumulating metabolites can impair the synthesis of *N*-acetylglutamate (NAG), the obligate activator of CPS1. Furthermore, some organic acids (e.g. methylcitrate in case of propionic acidemia or methylmalonic acidemia) inhibit the mitochondrial Krebs cycle and thus the availability of α-ketoglutarate as ammonia acceptor for glutamate synthesis. In addition, deficiency of acetyl-CoA or glutamate in the mitochondria or of substrates required for normal urea cycle function can lead to secondary hyperammonemia (see also Table 3).

Increased ammonia production caused by bacterial overgrowth can occur in bladders, uretero-sigmoid shunts or within the intestine. This can be seen in intestinal hypomotility of any cause, e.g. postoperative, in diabetic gastroparesis or myotonic muscular dystrophy. Besides, hyperammonemia can result if ammonia does not reach the detoxifying hepatocytes, e.g. in open Ductus venosus or portocaval shunting, and this might also contribute to the unclear phenomenon of "transient hyperammonemia of the newborn" (THAN). In addition, drugs can lead to hyperammonemia which was mostly reported secondary to valproate but other antiepileptic agents, L-asparaginase, furosemide and salicylic acid are also possible triggers of severe ammonia elevations [4, 7, 35].

Key points

- ➢ Primary hyperammonemia results from a defect of one of the urea cycle enzymes or transporters of ornithine or aspartate/glutamate
- ➢ Secondary hyperammonemia is caused by a defect outside the urea cycle that indirectly affects urea cycle function via inhibition or substrate deficiency

Clinical signs and symptoms

General aspects of signs and symptoms of hyperammonemia

Since ammonia is toxic mainly to the brain, most signs and symptoms of hyperammonemia are neurological. This is even true for "vomiting" as one of the most common signs of hyperammonemia at all ages which is not a pure abdominal sign but also a neurological sign.

Although non-specific at all ages, the clinical presentation will now be discussed in relation to certain age groups.

Signs and symptoms in neonates

Neonates have long been regarded as the group of patients most affected by hyperammonemia. This is not true with regard to the proportion of patients beyond the neonatal period but still partly true in clinical practice. In primary and secondary defects of the urea cycle, the pregnancy and first days of life will be uneventful because the maternal urea cycle will clear off any surplus nitrogen from the fetus. Depending on the specific defect, postnatal catabolism can lead to a clinically relevant ammonia increase within days. In severe primary defects of the urea cycle, e.g. if the intramitochondrial enzymes are defective, the asymptomatic interval may be as short as 24 h. Milder variants might only decompensate during severe states of catabolism in later life. Up to 50% of urea cycle patients present with respiratory alkalosis. Since septicemia is the most common differential diagnosis in a sick neonate and is in general accompanied by metabolic acidosis, presence of respiratory alkalosis should alert the clinician to perform an immediate re-evaluation including ammonia determinations. Confirmed septicemia does not exclude a primary hyperammonemic defect, since the catabolism associated with infection can provoke the manifestation of the genetic defect.

Signs and symptoms in infants and young children

Despite an uneventful postnatal period, affected infants and young children can manifest during any catabolic state. Especially in late infancy, protein anabolism is decreasing when postnatal growth slows down. This can be estimated from levels of urea production which are very low during rapid growth but increase after late infancy [13]. Any imbalance in energy demands, e.g. during febrile illness when nutritional intake is decreased, will result in endogenous protein catabolism and risk for hyperammonemia.

Signs and symptoms in older children and adults

Hyperammonemia can manifest for the first time at any age. Even an uneventful history with many catabolic situations but no signs of metabolic decompensation must not be interpreted as an exclusion of a primary or secondary urea cycle dysfunction. A very early in life self-chosen vegetarian diet

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