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Genetics of Hyperammonemia

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OVERVIEW

Background

Hyperammonemia is not a true disease; it is a sign that specific abnormalities that cause blood ammonia levels to become elevated may be present. Elevated blood ammonia levels cause a constellation of signs and symptoms that may appear to be a single disease. [1]

Normal blood ammonia levels range from 10-40 µmol/L, compared with a BUN level of 6-20 mg/dL. The total soluble ammonia level in a healthy adult with 5 L of circulating blood is only 150 mcg, in contrast to approximately 1000 mg of urea nitrogen present. Because urea is the end product of ammonia metabolism, the disparity in blood quantities of the substrate and product illustrates the following 2 principles:

- The CNS is protected from the toxic effects of free ammonia.
- The metabolic conversion system that leads to production of urea is highly efficient.

An individual is unlikely to become hyperammonemic unless the conversion system is impaired in some way. In newborns, this impairment is often the result of genetic defects, whereas, in older individuals, the impairment is more often the consequence of a diseased liver. However, a growing number of reports address adult-onset genetic disorders of the urea cycle in previously healthy individuals.

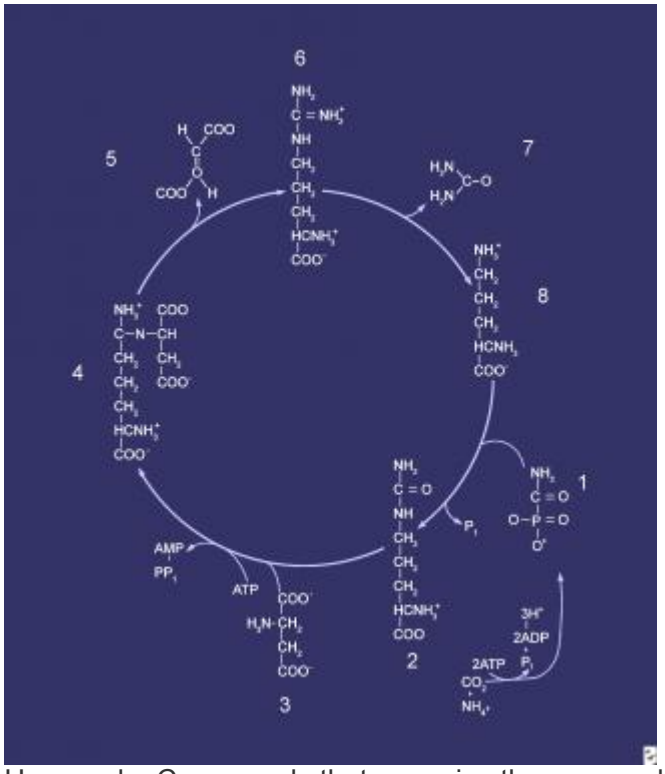
Pathophysiology

The true mechanism of neurotoxicity in hyperammonemia is not yet fully determined. Irrespective of the underlying cause, the clinical picture is relatively constant. This implies that the pathophysiologic mechanism, focusing on the CNS, is common to all individuals with hyperammonemia.

The normal process of removing the amino group present on all amino acids produces ammonia. The α -amino group is a catabolic key that protects amino acids from oxidative breakdown. Removing the α -amino group is essential for producing energy from any amino acid.

Under normal circumstances, both the liver and the brain generate ammonia in this removal process, substantially contributing to total body ammonia production. The urea cycle is completed in the liver, where urea is generated from free ammonia.

The hepatic urea cycle (see the image below) is the major route for disposal of waste nitrogen chiefly generated from protein and amino acid metabolism.



Urea cycle. Compounds that comprise the urea cycle are numbered sequentially, beginning with carbamyl phosphate. At the first step (1), the first waste nitrogen is incorporated into the cycle; also at this step, N-acetylglutamate exerts its regulatory control on the mediating enzyme, carbamyl phosphate synthetase (CPS). Compound 2 is citrulline, the product of condensation between carbamyl phosphate (1) and ornithine (8); the mediating enzyme is ornithine transcarbamylase. Compound 3 is aspartic acid, which is combined with citrulline to form argininosuccinic acid (4); the reaction is mediated by argininosuccinate (ASA) synthetase. Compound 5 is fumaric acid generated in the reaction that converts ASA to arginine (6), which is mediated by ASA lyase.

In the same context, low-level synthesis of certain cycle intermediates in extrahepatic tissues also makes a small contribution to waste nitrogen disposal. Two moles of waste nitrogen are eliminated with each mole of urea excreted. A portion of the cycle is mitochondrial in nature; mitochondrial dysfunction, whether genetically or pharmacologically induced, may impair urea production and result in hyperammonemia. Overall, activity of the cycle is regulated by the rate of synthesis of *N* -acetylglutamate (NAG), the enzyme activator that initiates incorporation of ammonia into the cycle.

The brain must expend energy to detoxify and to export the ammonia it produces. This is accomplished in the process of producing adenosine diphosphate (ADP) from ATP by the enzyme glutamine synthetase, which is responsible for mediating the formation of glutamine from an amino group. Synthesis of glutamine also reduces the total free ammonia level circulating in the blood; therefore, a significant increase in blood glutamine concentration can signal hyperammonemia.

The biologic requirement for tight regulation is satisfied because the capacity of the hepatic urea cycle exceeds the normal rates of ammonia generation in the periphery and transfer into the blood. Hyperammonemia never results from endogenous production in a state of health.

An elevated blood ammonia level, although it may be secondary, must never be ignored. Moreover, since the normal ureagenic capacity of the liver is so great in relation to physiologic load, such a finding points directly to an impairment of the urea cycle in the liver.

The CNS is most sensitive to the toxic effects of ammonia. Many metabolic derangements occur as a consequence of high ammonia levels, including alteration of the metabolism of important compounds, such as pyruvate, lactate, glycogen, and glucose. High ammonia levels also induce changes in *N* -methyl D-aspartate (NMDA) and gamma-aminobutyric acid (GABA) receptors and causes downregulation in astroglial glutamate transporter molecules.

As ammonia exceeds normal concentration, an increased disturbance of neurotransmission and synthesis of both GABA and glutamine occurs in the CNS. A correlation between arterial ammonia concentration and brain glutamine content in humans has been described. Moreover, brain content of glutamine is correlated with intracranial pressure. In vitro data also suggest that direct glutamine application to astrocytes in culture causes free radical production and induces the membrane permeability transition phenomenon, which leads to ionic gradient dissipation and consequent mitochondrial dysfunction.

Studies in mice suggest that increased ammonia concentration in brain causes upregulation of aquaporin-4, a water channel which has been associated with increased water permeability in other neurodisorders. [2, 3] However, the true mechanism for neurotoxicity of ammonia is not yet completely defined. The pathophysiology of hyperammonemia is that of a CNS toxin that causes irritability, somnolence, vomiting, cerebral edema, and coma that leads to death.

Epidemiology

Frequency

United States

The frequency of each genetic cause of hyperammonemia is undetermined because of the technical difficulties in accurately detecting each through an organized newborn screening program. The reported incidence of argininosuccinic acid synthase and argininosuccinic acid lyase deficiencies from a database of more than 6 million live births across the United States is 1 per 35,000 live births per year. [4] The combined incidence of urea cycle disorders has been estimated at approximately 1 per 20,000-25,000 live births. Providing incidence figures for clinically significant partial defects or secondary causes of hyperammonemia is not possible. Any severe impairment of liver function, whether temporary or permanent, can initiate the onset of hepatic encephalopathy.

International

A report from a single screening site in Germany, analyzing samples from almost 1.1 million newborns over a decade, detected a combined total of 11 cases of citrullinemia and argininosuccinic aciduria. [5] A second report indicates that the European incidence of all urea cycle disorders is in the range of 1:8000, a figure difficult to confirm through mass screening because of the aforementioned technical problems. [6]

Mortality/Morbidity

Progressive hyperammonemia, whether treated or not, eventually causes cerebral edema, coma, and death. A rapid diagnostic evaluation and alleviation of the cause must be accompanied by treatment.

Although the vast majority of morbidity associated with hyperammonemia derives from the primary cause, such as chronic liver disease, repeated hyperammonemic episodes can also cause morbidity. The result, given the direct toxicity of ammonia on the CNS, is a progressive decrease in intellectual function. Animal studies suggest actual cell death as the cause.

Sex

In the genetic forms of hyperammonemia, men and women are affected equally because almost all types are autosomal recessive traits. The only exception to equal sex distribution is X-linked ornithine

transcarbamylase (OTC) deficiency, the most common of the urea cycle disorders. OTC deficiency predominantly affects males, although female carriers have been clinically affected.

Acquired causes are distributed randomly between the sexes. However, some acquired causes, such as alcoholic cirrhosis, show a population distribution skewed by societal phenomena.

Age

Genetic causes of hyperammonemia manifest as a wide variety of conditions. The different presentations are categorized as catastrophic newborn, late-infantile, and adult. Each inherited disorder is reported in various clinical presentations. In some patients with adult-onset disease, no precedent sign of intellectual dysfunction was present, leading to the assumption that the disorder was truly latent until the first acute presentation.

Age of onset depends on the age and rate of progression of the underlying disease process. Impairments that must be considered range from hepatic necrosis with hepatocellular damage to inborn genetic disorders of the urea cycle. Although history and age of the patient are helpful to diagnosis, genetic causes must never be disregarded, irrespective of the stage of life. Data from a very large cohort of patients (260) with inherited urea cycle disorders showed a surprisingly high rate of initial onset beyond the neonatal period (66%). [7] Indeed, in a subgroup of 69 males with OTC deficiency, 35% presented when older than 2 years in this series.

Prognosis

In general, it is difficult to determine the prognosis for an individual with hyperammonemia. The extent of lasting damage done by a single episode of hyperammonemia may be trivial if the episode is mild and short-lived, whereas such situations, if repetitive, can cause extensive and permanent dysfunction. Likewise, a single occasion of severe hyperammonemia may cause irreversible damage and/or death. Age at onset is also an important factor in determination of likely recovery.

Clinical Presentation

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Media Gallery

- Urea cycle. Compounds that comprise the urea cycle are numbered sequentially, beginning with carbamyl phosphate. At the first step (1), the first waste nitrogen is incorporated into the cycle; also at this step, N-acetylglutamate exerts its regulatory control on the mediating enzyme, carbamyl phosphate synthetase (CPS). Compound 2 is citrulline, the product of condensation between carbamyl phosphate (1) and ornithine (8); the mediating enzyme is ornithine transcarbamylase. Compound 3 is aspartic acid, which is combined with citrulline to form argininosuccinic acid (4); the reaction is mediated by argininosuccinate (ASA) synthetase. Compound 5 is fumaric acid generated in the reaction that converts ASA to arginine (6), which is mediated by ASA lyase.

of 1

Tables

Back to List

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