Inborn Errors of Metabolism with Hyperammonemia

Urea Cycle Defects and Related Disorders

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KEYWORDS

• Hyperammonemia • Ammonia • Arginine • Citrulline • Liver • Urea cycle • Ornithine

KEY POINTS

- Symptoms of hyperammonemia include cerebral edema, lethargy, anorexia, hyperventilation or hypoventilation, hypothermia, seizures, neurologic posturing, and coma.
- Clinical awareness and suspicion of hyperammonemia is the most important component in the diagnosis and treatment of inborn errors of metabolism associated with elevated ammonia levels.
- For the pediatrician, recognition, stabilization, and rapid transport to a center with a metabolic specialist is the surest way to achieve an optimal outcome.
- Emergency management of hyperammonemia is based on 3 interdependent principles: physical removal of the ammonia by renal replacement therapy, reversal of the catabolic state, and pharmacologic scavenging of excess nitrogen.

INTRODUCTION

The urea cycle, first described by Krebs and Henseleit,[1] converts into urea the extra nitrogen produced by the breakdown of protein and other nitrogen-containing molecules (**Fig. 1**). A congenital or secondary deficiency of the urea cycle may, thus, result in the accumulation of ammonia and other precursor metabolites. Through a variety of mechanisms, hyperammonemia can cause cerebral edema, lethargy, anorexia, hyperventilation or hypoventilation, hypothermia, seizures, neurologic posturing, and coma.

The urea cycle as a nitrogen clearance system is limited primarily to the human liver and intestine with carbamyl phosphate synthetase (CPS1) and ornithine transcarbamylase (OTC) limited exclusively to those tissues. The enzymes downstream that process citrulline into arginine are ubiquitous in their distribution, because these enzymes participate in the production of nitric oxide (NO).

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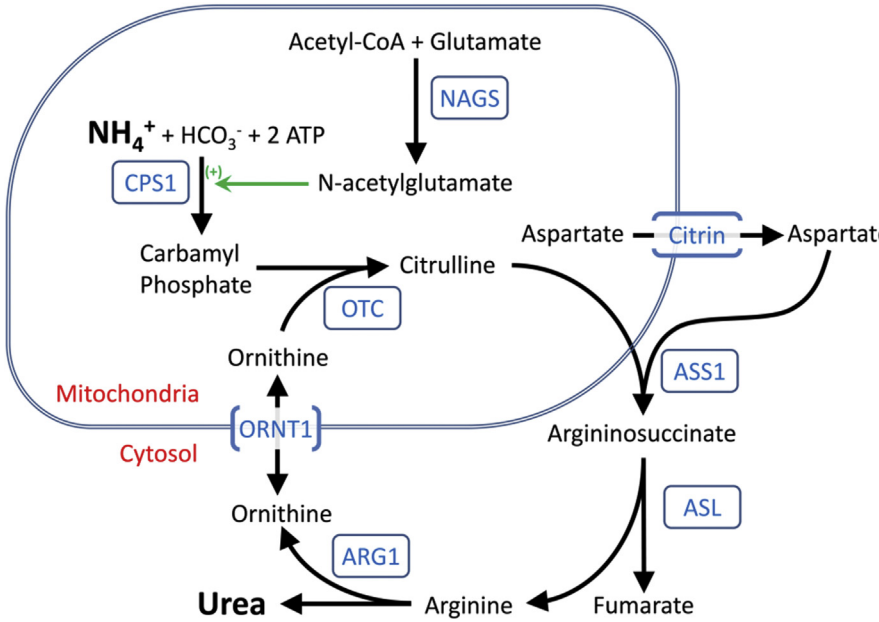

Fig. 1. The hepatic urea cycle. ARG1, arginase; ASL, argininosuccinic acid lyase; ASS1, argininosuccinic acid synthase; ATP, adenosine triphosphate; CoA, coenzyme A; CPS1, carbamyl phosphate synthetase 1; NAGS, *N*-acetylglutamate synthase; ORNT1, mitochondrial ornithine transporter 1; OTC, ornithine transcarbamylase.

A primary urea cycle disorder (UCD) results from an inherited defect in one of the 6 enzymes or 2 transporters of the urea cycle (see **Fig. 1**). Infants with near or total absence of activity of any of these proteins, in particular the first 4 urea cycle enzymes (CPS1, OTC, argininosuccinate synthase [ASS1], and argininosuccinate lyase [ASL]) or the cofactor producer (*N*-acetyl glutamate synthetase [NAGS]), often initially seem to be normal, but within days develop signs and symptoms of hyperammonemia. With partial urea cycle enzyme deficiencies, individuals may go decades before encountering an environmental stress that overwhelms their marginal ureagenesis capacity, resulting in a hyperammonemic episode. Commonly distributed, functional polymorphisms in the urea cycle may not result in hyperammonemia, but instead affect the production of downstream metabolic intermediates (such as arginine) during key periods of need. These variations in intermediate molecule supply can affect other metabolic pathways such as the production of NO from citrulline and arginine, and potentially the tricarboxylic acid cycle through aspartate and fumarate.

A secondary defect in the urea cycle may occur if there is a functional deficiency of substrates of one of the urea cycle enzymes. Examples include low intramitochondrial bicarbonate in carbonic anhydrase 5A deficiency, or low ornithine in lysinuric protein intolerance and neonatal ornithine aminotransferase deficiency. Additionally, inhibition of the cofactor producer, NAGS, is a proposed mechanism of urea cycle dysfunction in several conditions, including the organic acidemias, valproate toxicity, and chemotherapy-induced hyperammonemia. Furthermore, generalized liver dysfunction caused by toxin, infection, poor perfusion, or other inborn errors of metabolism, may impair urea cycle function and result in hyperammonemia (**Box 1**).