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Urea Cycle Disorders Overview

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Summary

Clinical characteristics. The urea cycle disorders (UCD) result from defects in the metabolism of waste nitrogen from the breakdown of protein and other nitrogen-containing molecules. Severe deficiency or total absence of activity of any of the first four enzymes (CPS1, OTC, ASS, ASL) in the urea cycle or the cofactor producer (NAGS) results in the accumulation of ammonia and other precursor metabolites during the first few days of life. Infants with a severe urea cycle disorder are normal at birth but rapidly develop cerebral edema and the related signs of lethargy, anorexia, hyper- or hypoventilation, hypothermia, seizures, neurologic posturing, and coma. In milder (or partial) deficiencies of these enzymes and in arginase (ARG) deficiency, ammonia accumulation may be triggered by illness or stress at almost any time of life. In these disorders the elevations of plasma ammonia concentration and symptoms are often subtle and the first recognized clinical episode may not occur for months or decades.

Diagnosis/testing. The diagnosis of a urea cycle disorder is based on clinical suspicion and biochemical and molecular genetic testing. A plasma ammonia concentration of 150 µmol/L or higher associated with a normal anion gap and a normal plasma glucose concentration is an indication for the presence of a UCD. Plasma quantitative amino acid analysis and measurement of urinary orotic acid can distinguish between the specific UCDs. A definitive diagnosis of a urea cycle defect depends on either molecular genetic testing or measurement of enzyme activity. Molecular genetic testing is possible for all urea cycle defects.

Genetic counseling. Deficiencies of CPS1, ASS1, ASL, NAGS, and ARG are inherited in an autosomal recessive manner. OTC deficiency is inherited in an X-linked manner. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk using molecular genetic testing is possible for any of the urea cycle disorders if the pathogenic variant(s) in the family are known.

Management. *Treatment of manifestations*: Acute severe hyperammonemia: Dialysis and hemofiltration to reduce plasma ammonia concentration; intravenous administration of arginine hydrochloride and nitrogen scavenger drugs to allow alternative pathway excretion of excess nitrogen; restriction of protein for 12 to 24 hours to reduce the amount of nitrogen in the diet; calories given as carbohydrates and fat; and physiologic stabilization with intravenous fluids and cardiac pressors while avoiding overhydration.

Prevention of primary manifestations: Long-term management: prevention of catabolism to avoid hyperammonemic episodes by dietary restriction of protein, use of specialized formulas, and use of oral nitrogen-scavenging drugs.

Prevention of secondary complications: Minimize risk of respiratory and gastrointestinal illnesses; routine immunizations; multivitamin and fluoride supplementation; appropriate use of antipyretics.

Surveillance: Routine monitoring by a physician experienced in the treatment of metabolic disorders.

Agents/circumstances to avoid: Valproic acid (Depakote®); prolonged fasting or starvation; intravenous steroids; large boluses of protein or amino acids.

Evaluation of relatives at risk: Identification of affected at-risk relatives before symptoms occur allows dietary therapy and other measures to prevent hyperammonemia.

Definition

The urea cycle:

- Is the sole source of endogenous production of arginine, ornithine, and citrulline;
- Is the principal mechanism for the clearance of waste nitrogen resulting from protein turnover;
- Is the principal mechanism for the metabolism of other nitrogenous metabolic compounds such as adenosine monophosphate;
- Includes enzymes that overlap with the nitric oxide production pathway (ASS and ASL).

The urea cycle comprises the following (Figure 1) [Krebs & Henseleit 1932]:

Figure 1.

The urea cycle (see Differential Diagnosis)

- Five catalytic enzymes:
  - Carbamoylphosphate synthetase I (CPS1)
  - Ornithine transcarbamylase (OTC)
  - Argininosuccinic acid synthetase (ASS1)
  - Argininosuccinic acid lyase (ASL)
  - Arginase (ARG)
- A cofactor-producing enzyme: N-acetyl glutamate synthetase (NAGS)

Urea cycle disorders (UCD) result from inherited deficiencies in the six enzymes of the urea cycle pathway (CPS1, OTC, ASS1, ASL, ARG, and NAGS).

The urea cycle also depends on two transporters (discussed in Differential Diagnosis). Abnormalities in these transporters can present with hyperammonemia.

- Two transporters:
  - Ornithine translocase (ORNT1)
  - Citrin

NAGS deficiency. Deficiency of this enzyme has been described in a number of affected individuals. Symptoms mimic those of CPS1 deficiency, as CPS1 is rendered inactive in the absence of NAGS [Caldovic et al 2003].

Carbamoylphosphate synthetase I deficiency (CPS1 deficiency) is the most severe of the urea cycle disorders. Individuals with complete CPS1 deficiency rapidly develop hyperammonemia in the newborn period. Children who are successfully rescued from crisis are chronically at risk for repeated bouts of hyperammonemia.

Ornithine transcarbamylase deficiency (OTC deficiency). Absence of OTC activity in males is as severe as CPS1 deficiency. Approximately 15% of carrier females develop hyperammonemia during their lifetime and many require chronic medical management for hyperammonemia. More recently it has been recognized that carrier females who have never had symptoms of overt hyperammonemia have deficiencies in executive function.

Citrullinemia type I (ASS1 deficiency). The hyperammonemia in this disorder can also be quite severe. Affected individuals are able to incorporate some waste nitrogen into urea cycle intermediates, which makes treatment slightly easier than in the other UCDs.

Argininosuccinic aciduria (ASL deficiency) can also present with rapid-onset hyperammonemia in the newborn period. This enzyme defect is past the point in the metabolic pathway at which all the waste nitrogen has been incorporated into the cycle. Some affected individuals develop chronic hepatic enlargement and elevation of transaminases. Liver biopsy shows enlarged hepatocytes, which may over time progress to fibrosis, the etiology of which is unclear. Affected individuals can also develop trichorrhexis nodosa, a node-like appearance of fragile hair that usually responds to arginine supplementation. Affected individuals who have never had prolonged coma nevertheless have been reported to have significant developmental disabilities [Summar 2001, Summar & Tuchman 2001, Nagamani et al 2012].

Arginase deficiency (hyperargininemia, ARG deficiency) is not typically characterized by rapid-onset hyperammonemia, however, some individuals present earlier with more severe symptoms [Jain-Ghai et al 2011]. Affected individuals develop progressive spasticity and can also develop tremor, ataxia, and choreoathetosis. Growth is also affected [Cederbaum et al 2004].

Clinical Manifestations of Urea Cycle Disorders

Severity of the urea cycle defect is influenced by the position of the defective enzyme in the pathway and the severity of the enzyme defect.

Severe deficiency or total absence of activity of any of the first four enzymes in the pathway (CPS1, OTC, ASS1, and ASL) or the cofactor producer (NAGS) results in the accumulation of ammonia and other precursor metabolites during the first few days of life.

Because no effective secondary clearance system for ammonia exists, complete disruption of this pathway results in the rapid accumulation of ammonia and development of related symptoms. Individuals with complete defects normally present in the newborn period, when the immaturity of the neonatal liver accentuates defects in the urea cycle enzymes [Pearson et al 2001, Summar 2001, Summar & Tuchman 2001]. Infants with a urea cycle disorder appear normal at birth but rapidly develop cerebral edema and the related signs of lethargy, anorexia, hyper- or hypoventilation, hypothermia, seizures, neurologic posturing, and coma.

recognized in a timely manner by the family and primary care physician. The typical initial symptoms of a child with hyperammonemia are nonspecific: failure to feed, loss of thermoregulation with a low core temperature, and somnolence [Summar 2001].

Symptoms progress from somnolence to lethargy and coma. Abnormal posturing and encephalopathy are often related to the degree of central nervous system swelling and pressure on the brain stem [Summar 2001]. About 50% of neonates with severe hyperammonemia may have seizures, some without overt clinical manifestations. Individuals with closed cranial sutures are at higher risk for rapid neurologic deterioration from the cerebral edema that results from ammonia elevation. Hyperventilation secondary to the effect of hyperammonemia on the brain stem, a common early finding in hyperammonemic attacks, results in respiratory alkalosis. Hypoventilation and respiratory arrest follow as pressure increases on the brain stem.

With rapid identification and current treatment strategies, survival of neonates with hyperammonemia has improved dramatically in the last few decades [Summar 2001, Summar & Tuchman 2001, Enns et al 2007 (full text), Summar et al 2008, Tuchman et al 2008, Krivitzky et al 2009]. However, hyperammonemia is not the only influence on intellectual outcome. Specifically, individuals with ASL deficiency appear to have intellectual disability that is out of proportion to their hyperammonemia [Ah Mew et al 2013].

In milder (or partial) urea cycle enzyme deficiencies, ammonia accumulation may be triggered by illness or stress at almost any time of life, including surgery, prolonged fasting, holidays, and the peripartum period, resulting in multiple mild elevations of plasma ammonia concentration. Hyperammonemia in the milder defects is typically less severe and the symptoms more subtle than the neonatal presentation of a UCD. In individuals with partial enzyme deficiencies, the first recognized clinical episode may be delayed for months or years. Although the clinical abnormalities vary somewhat with the specific urea cycle disorder, in most the hyperammonemic episode is marked by loss of appetite, vomiting, lethargy, and behavioral abnormalities [Gardeitchik et al 2012]. Sleep disorders, delusions, hallucinations, and psychosis may occur. An encephalopathic (slow-wave) EEG pattern may be observed during hyperammonemia and nonspecific brain atrophy may be seen subsequently on MRI.

Defects in the final enzyme in the pathway (ARG) cause hyperargininemia, a more subtle disorder involving neurologic symptoms; however, neonatal hyperammonemia has been reported (see Arginase Deficiency.)

Neurologic aspects of UCDs. Ammonia can cause brain damage through a variety of proposed mechanisms, a major component of which is cerebral edema. The specific roles of ammonia, glutamate, and glutamine in cerebral edema are still under investigation; they are thought to affect the aquaporin system and water and potassium homeostasis in brain [Lichter-Konecki 2008, Lichter-Konecki et al 2008, Albrecht et al 2010].

Damage resulting from acute hyperammonemia in infancy resembles that seen in hypoxic-ischemic events or stroke. Lacunar infarcts and white matter disruption are common findings.

Chronic hyperammonemia may disrupt ion-gradients and neurotransmitters, transport of metabolites, mitochondrial function, and the alpha-ketoglutarate/glutamate/glutamine ratio.

Seizures are common in acute hyperammonemia and may result from cerebral damage. Recent findings suggest that subclinical seizures are common in acute hyperammonemic episodes and their

of its effects on CPS1 function. See Management, Agents/Circumstances to Avoid.)

Newer neuroimaging techniques that provide information about the timing, extent, reversibility, and possible mechanism of neural injury in a noninvasive manner can be used as an adjunct to predict clinical and neurocognitive outcome [Gropman 2010, Bireley et al 2012, Gunz et al 2013].

The limitations of routine neuroimaging:

- Damage can only be detected at a macroscopic level, typically at a time when symptoms are already present.
- MRI findings may lag behind clinical changes.

Advanced imaging sequences such as magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), and functional magnetic resonance imaging (fMRI) provide additional details about the pattern and type of injury and have shed light on various neurologic problems seen in urea cycle disorders.

- **MRS.** In OTC deficiency, biochemical markers of brain injury resulting from hyperammonemia that can be measured quantitatively on 1H MRS include increased glutamine levels and depletion of myoinositol.
- **DTI**
  - In UCDs, DTI commonly shows a pattern of white matter injury affecting the cingulum, a major fiber bundle that underlies pathways involving working memory and attention.
  - In arginase deficiency, DTI demonstrates additionally decreased fiber density reflecting the predilection of corticospinal tracts to brain injury corresponding to the spastic diplegia observed in this disorder.
- **fMRI.** Persons with late-onset OTC deficiency, who have traditionally been considered intellectually normal, often show altered neural circuitry by fMRI when performing tasks requiring working memory and attention.

Historically the outcome of newborns with hyperammonemia was considered poor [Brusilow 1995]. More recent data from the NIH-sponsored longitudinal study on patients treated with the more recent protocols show IQ measures within a less severe range.

Table 1.

Cognitive and Adaptive Outcome in Children with UCD Age 3-16 Years

	Age Group	**Age 3-5 Years**		**Age 6-16 Years**	
	Age at Onset	**Neonatal [1] (n=5)**	**Late [2] (n=7)**	**Neonatal [1] (n=8)**	**Late [2] (n=39)**
	WASI/WPPSI-III [3] composite scores [4] (SD)				
	• **Verbal IQ**	81.3 (16.6)	101.7 (24.4)	72.9 (14.3)	94.3 (21.7)

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