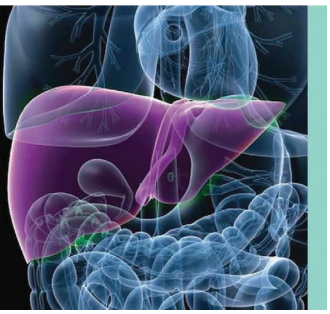

Hepatic Manifestations of Urea Cycle Disorders

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OVERVIEW

All tissues produce the neurotoxin ammonia as a by-product of amino acid metabolism. The primary route of ammonia removal in mammals is the hepatic urea cycle (UC), a series of biochemical reactions that enables urinary excretion of waste ammonia as urea. The urea cycle disorders (UCDs) are monogenic disorders caused by a deficiency of an enzyme or cellular transporter essential to ureagenesis (Fig. 1). The primary acute manifestations of UCDs are hyperammonemia, liver dysfunction, and encephalopathy. Common long-term sequelae are neurological deficits, cognitive impairments, and hepatic disease.[1] Prompt diagnosis and initiation of treatment are critical to survival and optimal neurocognitive outcome.[2]

EPIDEMIOLOGY AND GENETICS

UCDs affect all ethnicities and have an estimated US incidence of 1/35,000 births. Ornithine transcarbamylase (OTC) deficiency accounts for ~60% of cases.[3] UCDs are predominantly inherited in an autosomal recessive fashion with the notable exception of OTC, which is X linked. Null genetic variants, typically gene deletions, nonsense mutations, and frameshift mutations, result in near-complete enzyme deficiency and severe disease, whereas missense mutations are associated with partial enzyme deficiency and attenuated disease.[4]

DIAGNOSIS

UCDs may present at any age, even in adult life, but two-thirds occur in the neonatal period (Table 1). A major diagnostic advance is newborn screening for UCDs, which uses mass spectrometry to measure amino acids in presymptomatic neonates. Regrettably, the lack of a reproducible amino acid marker for OTC has confounded reliable presymptomatic screening for this disorder.[5] Symptomatic infants typically present with lethargy, seizures, hypotonia,

Abbreviations: ASL, Argininosuccinate lyase; ASS, Argininosuccinate synthase; CPSI, carbamoylphosphate synthetase-1; HHH, hyperammonemia, hyperornithemia, homocitrullinemia; IV, intravenous; MCT, medium-chain triglycerides; NAGS, N-acetylglutamate synthase; OTC, ornithine transcarbamylase; UC, urea cycle; UCD, urea cycle disorder.

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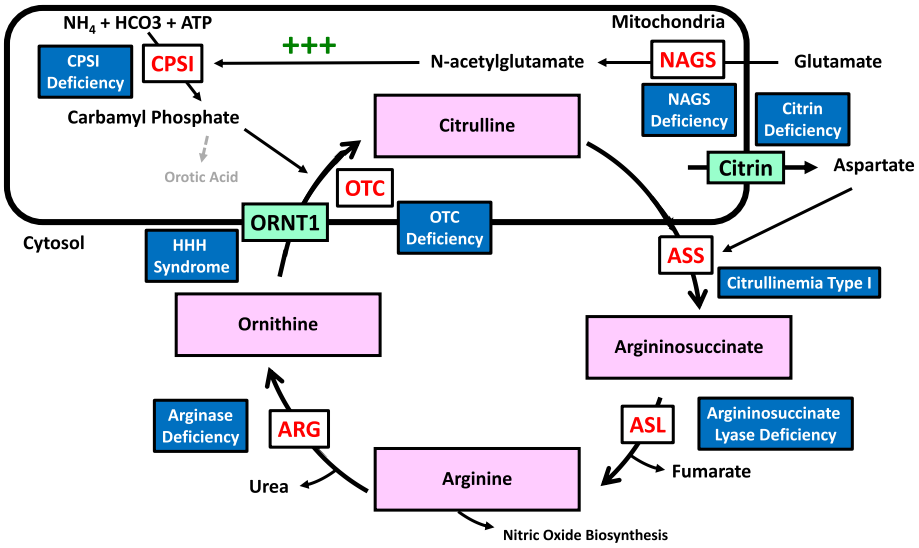

FIG 1 Schematic of the urea cycle. CPSI catalyzes the reaction of ammonium, bicarbonate, and ATP to form carbamyl phosphate, which combines with mitochondrial ornithine to generated citrulline in a reaction catalyzed by OTC. Aspartate is transported to the cytosol through the citrin carrier and combines with citrulline to form argininosuccinate in a reaction catalyzed by argininosuccinate synthetase. Argininosuccinate is converted to arginine by argininosuccinate lyase. Arginine can be used in nitric oxide biosynthesis or can be converted to urea and ornithine via arginase. Generated ornithine is transported into the mitochondria by the ornithine transporter to combine with carbamyl phosphate and generate citrulline and replenish the cycle. CPSI is the rate-limiting step in the urea cycle, and is allosterically activated by N-acetylglutamate, which is generated from glutamate by NAGS. Abbreviations: ARG: arginase; ASL: argininosuccinate lyase; ASS: argininosuccinate synthetase; CPSI: carbamylphosphate synthetase-1; HHH: Hyperornithinemia-hyperammonemia-homocitrullinuria; NAGS: N-acetylglutamate synthetase; ORNT1: ornithine transporter; OTC: ornithine transcarbamylase.

poor feeding, and tachypnea in the first days to weeks of life.[1] These signs often prompt an erroneous diagnosis of neonatal sepsis, a confusion that may be compounded by the absence in UCDs of other stigmata of metabolic disease, such as anion gap acidosis, lacticemia, and hypoglycemia. In fact, many symptomatic neonates demonstrate a respiratory alkalosis. The biochemical hallmark of UCDs is hyperammonemia, which is often extreme. Ammonia levels less than 100 μmol/L are considered normal in neonates, whereas 60 μmol/L is considered the upper limit of normal after 1 month of age. Plasma ammonia samples preferably should be collected from a free-flowing puncture with no tourniquet, stored on ice, and run immediately on receipt by the laboratory. Improper sample collection or handling may lead to falsely elevated values.

Individuals with partial enzyme deficiencies may present more mildly, with their first symptoms emerging after the neonatal period. Common childhood manifestations include global developmental delay, neuroregression, spasticity, epilepsy, psychiatric symptoms, growth failure, and aminotransferase elevation. Many children and adults self-restrict intake of high-protein foods, such as meat and dairy, as a learned response to feeling unwell after protein-rich meals. Children and adults with UCDs are at risk for acute-onset encephalopathy, seizure, and coma in the setting of critical illness or exposure to certain medications, such as systemic steroids or valproate.[6]

Adult women are at particular risk for postpartum hyperammonemic crises due to the increased protein load from uterine remodeling and red blood cell turnover.[7,8] Gastric bypass surgery can also unmask an underlying UCD by inducing a catabolic state and altering protein absorption. Other triggers of hyperammonemia in adults with UCDs include short bowel disease and gastrointestinal bleeding.[8]

Diagnosis of UCDs in children and adults is established using complementary biochemical testing (measurement of plasma ammonia, plasma amino acids, urine organic acids, and urine orotic acid testing), as well as gene sequencing (Fig. 2).[9]

TREATMENT

Acute hyperammonemia causes cerebral accumulation of glutamate and glutamine, leading to both excessive

TABLE 1. UCDs

Disorder Type	Disease	Causal Gene	Inheritance	Classical Phenotype	Mild/Late-Onset Disease	Liver Disease
Proximal UC defect	NAGS deficiency	*NAGS*	Autosomal recessive	Hyperammonemia, encephalopathy, seizures, developmental delay, regression	Developmental delay, episodic hyperammonemia	Steatosis
	CPSI deficiency	*CPSI*	Autosomal recessive	Hyperammonemia, encephalopathy, seizures, developmental delay, regression	Episodic hyperammonemia	Acute liver failure, steatosis, fibrosis
Distal UC defect	OTC deficiency	*OTC*	X-linked recessive	Hyperammonemia, encephalopathy, seizures, neuropsychiatric symptoms	Neuropsychiatric disturbances, neurocognitive deficits, seizures, encephalopathy	Hepatitis, synthetic liver dysfunction
	Citrullinemia type I	*ASS*	Autosomal recessive	Hyperammonemia, encephalopathy, seizures, developmental delay, regression	Pregnancy-induced acute liver failure, neurocognitive disturbances, episodic hyperammonemia	Acute liver failure, steatosis, fibrosis, hepatocellular carcinoma
	Argininosuccinate lyase deficiency	*ASL*	Autosomal recessive	Hyperammonemia, encephalopathy, seizures, developmental delay, regression, trichorrhexis nodosa, brittle hair, hypertension	Neurocognitive disturbances, episodic hyperammonemia	Hepatomegaly, hepatic fibrosis, cirrhosis, portal hypertension, hepatocellular carcinoma
	Arginase deficiency	*ARGI*	Autosomal recessive	Regression, progressive spasticity, seizures, hyperammonemia (rarer)	Developmental delay, regression, spasticity, episodic hyperammonemia	Hepatomegaly, hepatitis, steatosis, fibrosis, hepatocellular carcinoma
Transporter defect	HHH syndrome	*SLC25A15*	Autosomal recessive	Hyperammonemia, encephalopathy, seizures, spasticity, regression	Neurocognitive deficits, ataxia, spasticity, seizures	Liver dysfunction, coagulopathy, steatosis, fibrosis (mild)
	Citrin deficiency (citrullinemia type II)	*SLC25A13*	Autosomal recessive	Liver disease, poor growth	Neuropsychiatric disturbances, neurocognitive deficits, pancreatitis	Cholestasis, hepatomegaly, steatosis, fibrosis

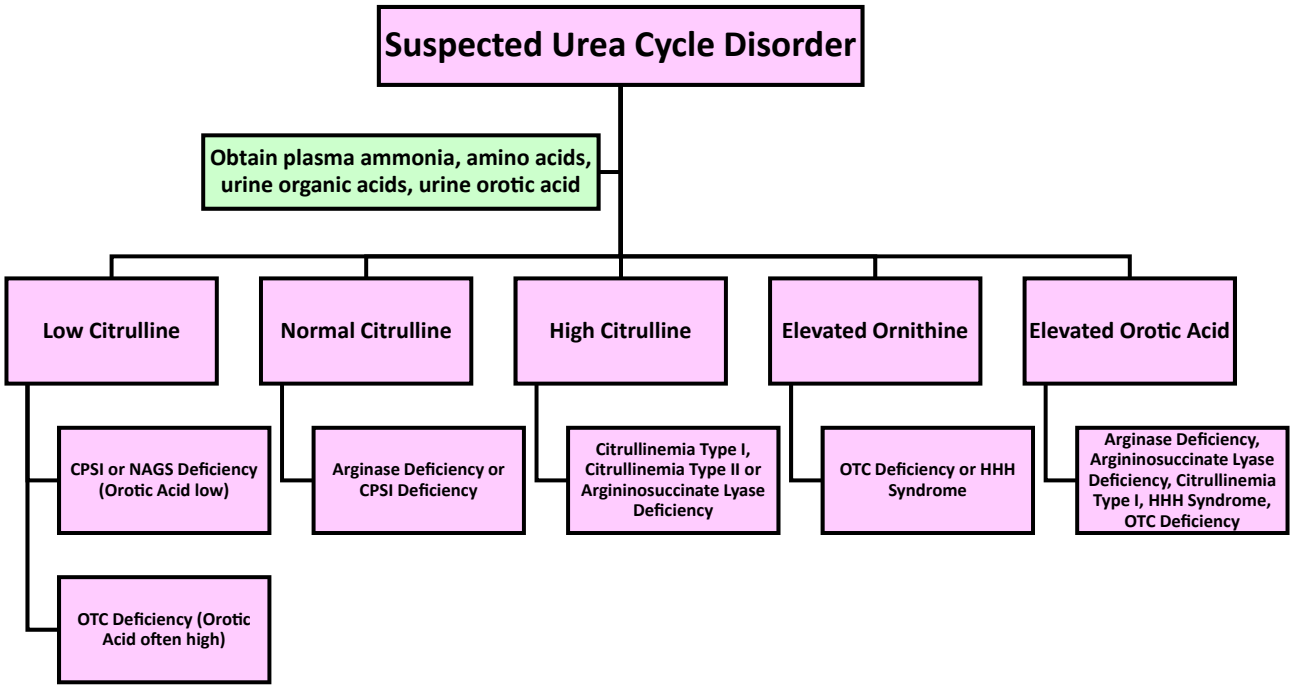

FIG 2 Diagnostic algorithm for UC diagnosis. Assessment should begin with evaluation of plasma amino acids, urine organic acids, and urine orotic acid. Citrulline level can help distinguish CPSI, OTC, citrullinemia I, citrullinemia II, and argininosuccinate lyase deficiency. Ornithine level can help diagnose OTC deficiency and HHH syndrome. Orotic acid levels can help diagnose arginase deficiency, argininosuccinate lyase deficiency, citrullinemia type I, HHH syndrome, and OTC deficiency.

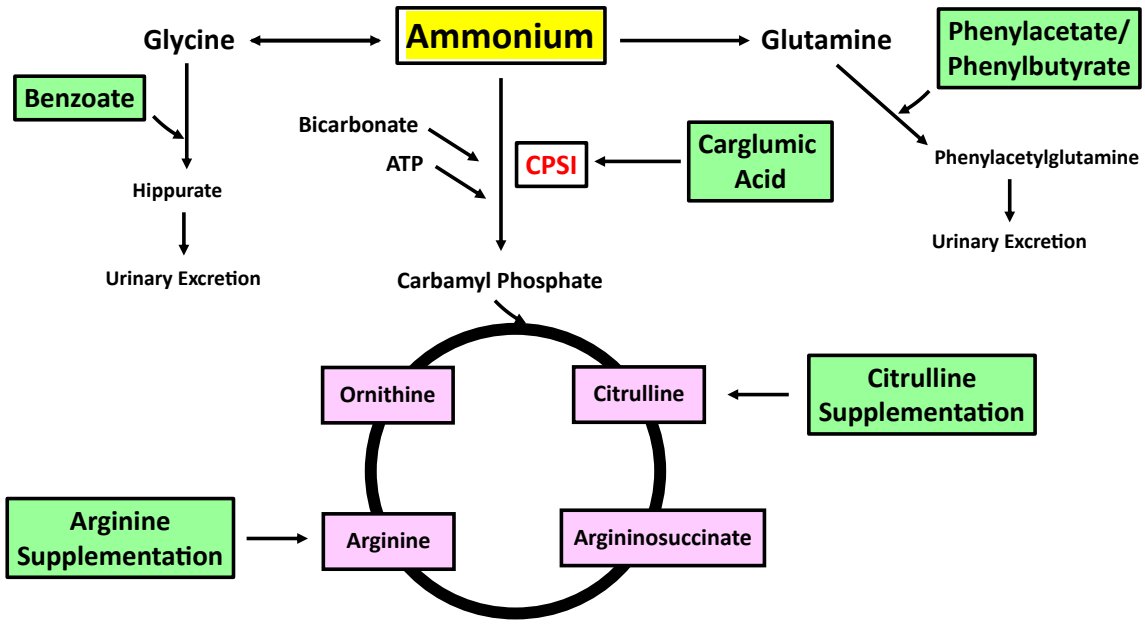

FIG 3 Treatments modalities for UCDs. Benzoate complexes with glycine and is converted to Hippurate, which can be excreted in urine, bypassing the urea cycle. Phenylacetate and its precursor phenylbutyrate complex to glutamine, forming phenylacetylglutamine, which is excreted in urine. Carglumic acid, like NAGS, is an allosteric activator of CPSI, increasing flux through the urea cycle, and is useful in proximal urea cycle disorders. Arginine and citrulline supplementation replenishes deficient urea cycle substrates. Importantly, arginine supplementation is contraindicated in arginase deficiency. Abbreviation: CPSI, arbomylphosophate synthetase I.

TABLE 2. TREATMENTS FOR UCDs

Disorder Type	Disease Name	Acute Treatment	Chronic Treatment	Surveillance
Proximal UC defects	NAGS deficiency	Halt protein intake, nitrogen scavengers, IV dextrose, carglumic acid	Protein restriction, carglumic acid	Monitor liver function, nutritional status, and vitamin deficiencies
	CPSI deficiency	Halt protein intake, IV scavengers, IV arginine, dextrose-containing fluids	Protein restriction, arginine or citrulline supplementation, hospitalization for dextrose-containing fluids with illness	Monitor liver function, nutritional status, and vitamin deficiencies
Distal UC defects	OTC deficiency	Halt protein intake, IV scavengers, IV arginine, dextrose-containing fluids	Protein restriction, arginine or citrulline supplementation, nitrogen scavengers, liver transplant	Monitor liver function, nutritional status, and vitamin deficiencies
	Citrullinemia type I	Halt protein intake, IV scavengers, IV arginine, dextrose-containing fluids	Protein restriction, nitrogen scavengers, arginine supplementation, hospitalization for dextrose-containing fluids with illness, citrulline is contraindicated	Monitor liver function, nutritional status, and vitamin deficiencies
	Argininosuccinate lyase deficiency	Halt protein intake, IV scavengers, IV arginine, dextrose-containing fluids	Protein restriction, nitrogen scavengers, arginine supplementation, hospitalization for dextrose-containing fluids with illness	Monitor liver function, fibrosis, hepatocellular carcinoma, vitamin deficiencies, nutritional status
	Arginase deficiency	Arginine and citrulline are contraindicated	Protein restriction, nitrogen scavengers, arginine and citrulline are contraindicated	Monitor for movement disorder, liver function, liver fibrosis, nutritional status, and vitamin deficiencies
Transporter defect	HHH syndrome	Halt protein intake, IV scavengers, IV arginine, dextrose-containing fluids	Protein restriction, nitrogen scavengers, ornithine supplementation	Monitor liver function, fibrosis, hepatocellular carcinoma, vitamin deficiencies, nutritional status
	Citrin deficiency (citrullinemia type II)	Protein- and lipid-rich diet, IV nitrogen scavengers, arginine supplementation	Lipid- and protein-rich diet, MCT oil, galactose-free diet, nitrogen scavengers, arginine supplementation, sodium pyruvate supplementation	Monitor liver function, screen for steatosis, monitor for zinc deficiency

activation of glutamatergic receptors and increased osmotic pressure. The result is encephalopathy, often with seizures, brain swelling, hypoxic injury, and ultimately, neuronal death. Chronic hyperammonemia leads to down-regulation of glutamate receptors and increased GABAergic signaling, causing neurocognitive decline.[10] Management of patients with UCDs focuses on the prevention of both acute and chronic hyperammonemia.

The mainstay of treatment is a protein-restricted diet to decrease the nitrogen load. Most patients also use oral nitrogen scavengers (sodium benzoate and glycerol phenylbutyrate), which provide a route other than the defective UC for the elimination of waste nitrogen, thereby lessening the risk for development of hyperammonemia. An accessory intervention is supplementation of deficient UC intermediates, such as arginine and citrulline. For individuals with a deficiency of *N*-acetylglutamate synthase, one of the proximal UC defects, dramatic improvement is realized by treatment with *N*-carbamylglutamate (Carbaglu), a synthetic analogue of *N*-acetylglutamate, which is an obligatory effector of the hepatic UC. Rarely, lactulose is given to decrease the nitrogen load from gut flora (Table 2 and Fig. 3).[9] Routine surveillance includes blood pressure measurements; assessment of nutritional status through measurement of the level of blood albumin, amino acids, and vitamins; and surveillance of liver function and bone health. Even with careful management and adherence to medical protocols, some patients may progress to liver steatosis, fibrosis, cirrhosis, portal hypertension, and hepatocellular carcinoma. Liver fibrosis and malignancy are of particular concern for individuals with argininosuccinate lyase deficiency, likely caused by the hepatotoxicity of the accumulating intermediate argininosuccinate.[9]

Acute hyperammonemic crises are treated with elimination of dietary protein and infusion of intravenous (IV)

dextrose (most commonly 10% dextrose). Importantly, complete protein restriction should last no longer than 24 to 48 hours to avoid paradoxical hyperammonemia from essential amino acid deficiency and consequent muscle catabolism. In addition, patients with neurological symptoms of hyperammonemia may require IV sodium phenylacetate as a nitrogen scavenger and IV (or enteric) administration of citrulline and/or arginine. Severe and refractory hyperammonemia may require hemodialysis.[1,9]

The only "curative" therapy for UCDs is liver transplantation, which replaces the impaired UC; however, this does not reverse past neurological damage.

CONSIDERATIONS FOR PROLONGED SURVIVAL IN UCDs

The UCDs first were described about 50 years ago. At that time, the outlook was dire for babies with the classical, severe disease. Few survived to adulthood. The development of special low-protein metabolic foods, nitrogen scavengers, and liver transplantation have enabled long-term survival for most of these infants. Of course, survival is not cost-free, and we now recognize an array of complications that afflict older children and adults, including hypertension from impaired nitric oxide generation, chronic kidney disease and electrolyte abnormalities, often profound cognitive impairment, a distinct neuropsychiatric profile, and a hepatopathy that ranges from clinically silent aminotransferase elevation to cholestasis, steatosis, fibrosis, cirrhosis, portal hypertension, and hepatocellular carcinoma (Table 2).[11]

Liver disease in UCDs likely results from chronic accumulation of amino acids such as glutamine, toxic products such as argininosuccinate and guanidino compounds, ongoing steatosis and glycogen deposition, a deficiency of essential amino acids and nitric oxide, and a failure of adequate adenosine triphosphate production consequent to mitochondrial dysfunction.[11]

As women with UCDs attain reproductive age, there is a concomitant need for genetic counseling and careful monitoring during pregnancy and the postpartum period.

CONCLUSIONS

Prompt diagnosis and treatment of UCDs improves outcome. These disorders should be considered in any patient presenting with unexplained developmental regression, encephalopathy (especially if recurrent), seizures, movement disorder, or liver disease. Despite advances in the diagnosis and treatment of UCDs, these disorders remain difficult to manage and are associated with significant neurological and hepatic morbidity and mortality. Liver transplantation corrects hyperammonemia but cannot reverse past neurological damage. Liver-directed gene therapy research is actively ongoing as an alternative to transplantation.

CORRESPONDENCE

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