Urea Cycle Disorders: Diagnosis, Pathophysiology, and Therapy*†

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Encephalopathy at any age may herald hyperammonemia. Consider this diagnosis early in the case of encephalopathic symptoms.

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DIAGNOSIS

Urea cycle disorders are characterized by the triad of encephalopathy, respiratory alkalosis, and hyperammonemia.

To prevent brain damage secondary to cerebral edema and increased intracranial pressure, a urea cycle disorder should be considered as a diagnostic possibility in any patient of any age, including adults[1] with occult encephalopathy. With monotonous regular-

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ity the hyperammonemic encephalopathy characteristic of urea cycle disorders is manifested by progressive lethargy, vomiting, irritability, and in older children and adults, ataxia and combative and bizarre behavior.

Included in the evaluation of such signs and symptoms should be measurement of blood gases and the plasma ammonium level. The finding of a respiratory alkalosis (frequently ignored even when measured!) early in the course is almost pathognomonic for a urea cycle disorder in such a setting. (A metabolic acidosis associated with hyperammonemia is more likely to be associated with one of the many organic acidoses, although in the later stages of hyperammonemia when brain stem compression and hemodynamic instability ensue, metabolic acidosis is common in urea cycle disorders.) Once hyperammonemia has been identified, aggressive diagnostic (quantitative analysis of plasma amino acids and urine orotate and qualitative analysis of urine for organic acids by gas chromatography and mass spectroscopy [GC/MS; the last to exclude other metabolic diseases]) and therapeutic measures (parenteral nutrition with high carbohydrate and zero protein and intravenous sodium benzoate and sodium phenylacetate) and, when necessary, hemodialysis should be started on an emergency basis. For very severe hyperammonemic encephalopathy (as occurs in neonates), hemodialysis may be the initial treatment of choice.

Symptomatic hyperammonemia approaches the seriousness of uncontrolled hemorrhage as a medical emergency.

EPIDEMIOLOGY

As a group, urea cycle disorders may be as common as many well-known diseases.

Until relatively recently, urea cycle disorders were thought to be rare diseases occurring in the newborn period[2] and thus of principal interest to neonatologists and biochemical geneticists. However, the experience of this center over the past 20 years suggests that urea cycle disorders are not only more common than previously suspected but are often manifested after the neonatal period. Table 1 demonstrates that 545 cases of urea cycle disorders were referred to the Johns Hopkins Hospital (JHH) over a 20-year period. It is apparent that ornithine transcarbamylase (OTC) deficiency (OTCD) is the most common of the urea cycle disorders, presumably because it is inherited as an X-linked trait (the others are inherited as autosomal recessive traits) and is expressed in some heterozygous females. The overall incidence of urea cycle disorders may be estimated by combining these data with those reported by

TABLE 1.
Distribution of Urea Cycle Cases Referred to The Johns Hopkins Hospital From 1974 to 1994*

Enzyme Deficiency	Number of Cases Referred
Carbamyl phosphate synthetase (CPS)	69
Ornithine transcarbamylase (OTC)	334
Argininosuccinic acid synthetase (AS)	74
Argininosuccinase (AC)	57
Arginase (A)	11
Total	545

*From Brusilow SW, Maestri NE: The phenotype of women who have a mutation at the ornithine transcarbamylase locus, in Platt L (ed): *Effects of Genetic Disorders on Pregnancy Outcome*. London, Parthenon Publishing Group, 1996. Used by permission.

Levy et al.,[3] in which it was found that by screening urine for argininosuccinate (ASA) at 4 weeks of age, an incidence of argininosuccinase deficiency (ALD) of 1 per 70,000 could be ascertained. Assuming that the number of ALD cases shown in Table 1 occurred at that incidence* and that the distribution of the other urea cycle disorders reflects their incidence relative to ALD, an estimate of the incidence of each of the urea cycle disorders may be calculated (Table 2). Notwithstanding considerable ambiguity of these derived figures, they do suggest that urea cycle disorders are as or more common than many diseases regularly part of differential diagnostic schemes. For example, the estimated incidence of all urea cycle disorders is approximately 1 per 8,000, with OTCD having an incidence of 1:14,000. These estimates compare favorably with those of acute leukemia and lymphoma, which are reported to have incidences of 1 per 25,000 and 1 per 75,000, respectively[4]; with end-stage renal disease in children, which has an incidence of 1 per 100,000[5]; and with juvenile rheumatoid arthritis, which has an incidence of 1 per 8,000.[6]

Table 3 describes the distribution of OTCD cases. Notwith-

*It should be noted that the number of referred cases of ALD is lower relative to the other diseases that are referred to this center as part of an investigational drug protocol. However, this may be corrected by the under-reporting of neonatal onset cases by Levy et al.[3]

TABLE 2.
Estimation of the Incidence of Each Urea Cycle Disorder Based on Its Incidence Relative to Argininosuccinase Deficiency

Enzyme Deficiency	Incidence
Carbamyl phosphate synthetase	1 per 62,000
Ornithine transcarbamylase	1 per 14,000
Argininosuccinate synthetase	1 per 57,000
Argininosuccinase	1 per 70,000
Arginase	1 per 363,000
All urea cycle disorders	1 per 8,200

standing past attention to the catastrophic manifestation of the neonatal form of the disease, 60% of referred patients have the late-onset form, 66% of whom are females who have a mutation at the *OTC* locus. That OTCD is not just a disease of male neonates and females is emphasized by the 66 cases of late-onset OTCD in males. It is presumed that the spectrum of disease seen in males with OTCD is a function of the variety and dispersion of mutations at the OTC locus of their single X chromosome, the mutations having different effects on OTC activity. Although the different mutations at the *OTC* locus may contribute to the spectrum of disease

TABLE 3.
Distribution of Cases of Ornithine Transcarbamylase Deficiency

Distribution	Number of Cases
Neonatal onset	134
Late onset	200
Males	
<18 yr	61
>18 yr	5
Females	
<18 yr	102
>18 yr	21
Unknown age	11
Total cases	334

seen in females, their variability is more likely a consequence of the proportion of hepatocytes in which the active X chromosome carries the normal or mutant *OTC* gene.

Case Studies

Case 1.—*A 6-year-old girl had multiple episodes of respiratory alkalosis, encephalopathy, and hyperammonemia. Ornithine transcarbamylase deficiency was diagnosed after a 10-month delay.*

This was the first JHH admission for this five-year-old girl born in 1986. She was the full-term product of an uneventful pregnancy and delivery and had normal developmental milestones. At 3½ years of age she was brought to her local emergency room with a chief complaint of listlessness and unintelligible speech for 48 hours. Physical examination revealed a temperature of 99.1° F, with otherwise normal vital signs. Neurologic examination revealed a very quiet child with a normal gait, a supple neck, and infrequent verbalizations that were unintelligible. Routine laboratory findings were all within normal limits. She was seen in follow-up 24 hours later and was thought to be normal. Her speech had recovered and her activity had returned toward normal but was still thought by the mother to be "quiet."

Six months later, at age 4, she was again brought to the emergency room with a chief complaint of restlessness, unsteady gait, and thrashing uncontrollably on her bed. Physical examination revealed normal vital signs and a hyperactive, confused child with ataxia and no coherent speech. The immediate impression was a posterior fossa lesion or an underlying metabolic disease; measurement of plasma ammonium and amino acids was recommended. Laboratory studies (venous blood) revealed a plasma ammonium level of 148 μmol/L (normal, <35), pH of 7.47, a P_{CO_2} of 27 mm Hg, and an HCO_3 concentration of 19 mmol/L. A computed tomographic (CT) scan of the brain was within normal limits. Her plasma amino acids revealed a glutamine level of 1,347 μmol/L (normal, 337 to 673) and a citrulline level of 20 μmol/L (normal, 10 to 30).

She was transferred to a tertiary care regional medical center where the previously noted physical findings were unchanged. Her laboratory (venous blood) values revealed a plasma ammonium level of 192 μmol/L, a pH of 7.44, and a P_{CO_2} of 30 mm Hg. Repeat CT of the head was again negative; magnetic resonance imaging (MRI) of the head was negative. The lead level, sympathetic amine levels, drug screen, and a urinary organic acid profile were all negative, or normal. The impression was "most likely diagnosed as a postinfectious encephalopathy." A genetics consultation was obtained and offered the following comment: "Elevated ammonia suggests possibility of metabolic cause. Ammonia tests, however, are

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