434e Inherited Disorders of Amino Acid Metabolism in Adults

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Amino acids are not only the building blocks of proteins but also serve as neurotransmitters (glycine, glutamate, γ-aminobutyric acid) or as precursors of hormones, coenzymes, pigments, purines, or pyrimidines. Eight amino acids, referred to as *essential*, cannot be synthesized by humans and must be obtained from dietary sources. The others are formed endogenously. Each amino acid has a unique degradative pathway by which its nitrogen and carbon components are used for the synthesis of other amino acids, carbohydrates, and lipids. Disorders of amino acid metabolism and transport (Chap. 435e) are individually rare—the incidences range from 1 in 10,000 for cystinuria or phenylketonuria to 1 in 200,000 for homocystinuria or alkaptonuria—but collectively, they affect perhaps 1 in 1000 newborns. Almost all are transmitted as autosomal recessive traits.

The features of inherited disorders of amino acid catabolism are summarized in Table 434e-1. In general, these disorders are named for the compound that accumulates to highest concentration in blood (*-emias*) or urine (*-urias*). In the aminoacidopathies, the parent amino acid is found in excess, whereas products in the catabolic pathway accumulate in organic acidemias. Which compound(s) accumulates depends on the site of the enzymatic block, the reversibility of the reactions proximal to the lesion, and the availability of alternative pathways of metabolic "runoff." Biochemical and genetic heterogeneity are common. Five distinct forms of hyperphenylalaninemia, nine forms of homocystinuria, and methylmalonic acidemia are recognized. Such heterogeneity reflects the presence of a large array of molecular defects.

The manifestations of these conditions differ widely (Table 434e-1). Some, such as sarcosinemia, produce no clinical consequences. At the other extreme, complete deficiency of ornithine transcarbamylase is lethal in the untreated neonate. Central nervous system (CNS) dysfunction, in the form of developmental retardation, seizures, alterations in sensorium, or behavioral disturbances, is present in more than half the disorders. Protein-induced vomiting, neurologic dysfunction, and hyperammonemia occur in many disorders of urea cycle intermediates. Metabolic ketoacidosis, often accompanied by hyperammonemia, is a frequent presenting finding in disorders of branched-chain amino acid metabolism. Some disorders produce focal tissue or organ involvement such as liver disease, renal failure, cutaneous abnormalities, or ocular lesions.

The analysis of plasma amino acids (by ion-exchange chromatography), urine organic acids (by gas chromatography/mass spectrometry), and plasma acylcarnitine profile (by tandem mass spectrometry) is commonly used to diagnose and monitor most of these disorders. The diagnosis is confirmed by enzyme assay on cells or tissues from the patients or by DNA testing. The clinical manifestations in many of these conditions can be prevented or mitigated if a diagnosis is achieved early and appropriate treatment (e.g., dietary protein or amino acid restriction or vitamin supplementation) is instituted promptly. For this reason, newborn screening programs seek to identify several of these disorders. Infants with a positive screening test need additional metabolic testing (usually suggested by the newborn screening program) to confirm or exclude the diagnosis. Confirmed cases should be referred to a metabolic center for initiation of therapy. The parents need to be counseled about the recurrence risk of the disease in future pregnancies. In some cases, parents need testing to exclude metabolic alterations seen in carriers for some of these disorders (such as some forms of homocystinuria) or because they might have a disorder themselves (such as glutaric acidemia type 1, methylcrotonyl coenzyme A carboxylase deficiency, or fatty acid oxidation defects). Some metabolic disorders can remain asymptomatic until adult age, presenting only when fasting or severe stress require full activity of affected metabolic pathways to provide energy.

Selected disorders that illustrate the principles, properties, and problems presented by the disorders of amino acid metabolism are discussed in this chapter.

THE HYPERPHENYLALANINEMIAS

The hyperphenylalaninemias (Table 434e-1) result from impaired conversion of phenylalanine to tyrosine. The most common and clinically important is *phenylketonuria* (frequency 1:10,000), which is an autosomal recessive disorder characterized by an increased concentration of phenylalanine and its by-products in body fluids and by severe mental retardation if untreated in infancy. It results from reduced activity of phenylalanine hydroxylase. The accumulation of phenylalanine inhibits the transport of other amino acids required for protein or neurotransmitter synthesis, reduces synthesis and increases degradation of myelin, and leads to inadequate formation of norepinephrine and serotonin. Phenylalanine is a competitive inhibitor of tyrosinase, a key enzyme in the pathway of melanin synthesis, and accounts for the hypopigmentation of hair and skin. Untreated children with classic phenylketonuria are normal at birth but fail to attain early developmental milestones, develop microcephaly, and demonstrate progressive impairment of cerebral function. Hyperactivity, seizures, and severe intellectual disability are major clinical problems later in life. Electroencephalographic abnormalities; "mousy" odor of skin, hair, and urine (due to phenylacetate accumulation); and a tendency to develop hypopigmentation and eczema complete the devastating clinical picture. In contrast, affected children who are detected and treated at birth show none of these abnormalities.

TREATMENT PHENYLKETONURIA

To prevent intellectual disability, diagnosis and initiation of dietary treatment of classic phenylketonuria must occur before the child is 2 weeks of age. For this reason, most newborns in North America, Australia, and Europe are screened by determinations of blood phenylalanine levels. Abnormal values are confirmed using quantitative analysis of plasma amino acids. Dietary phenylalanine restriction is usually instituted if blood phenylalanine levels are >360 μmol/L (6 mg/dL). Treatment consists of a special diet low in phenylalanine and supplemented with tyrosine, since tyrosine becomes an essential amino acid in phenylalanine hydroxylase deficiency. With therapy, plasma phenylalanine concentrations should be maintained between 120 and 360 μmol/L (2 and 6 mg/dL). Dietary restriction should be continued and monitored indefinitely. Some patients with milder forms of phenylketonuria (phenylalanine <1200 μm at presentation) show increased tolerance to dietary proteins and improved metabolic control when treated with tetrahydrobiopterin (5–20 mg/kg per day), an essential cofactor of phenylalanine hydroxylase.

A number of women with phenylketonuria who have been treated since infancy will reach adulthood and become pregnant. If maternal phenylalanine levels are not strictly controlled before and during pregnancy, their offspring are at increased risk for congenital defects and microcephaly (*maternal phenylketonuria*). After birth, these children have severe intellectual disability and growth retardation. Pregnancy risks can be minimized by continuing lifelong phenylalanine-restricted diets and assuring strict phenylalanine restriction 2 months prior to conception and throughout gestation.

THE HOMOCYSTINURIAS (HYPERHOMOCYSTEINEMIAS)

The homocystinurias are nine biochemically and clinically distinct disorders (Table 434e-1) characterized by increased concentration of the sulfur-containing amino acid homocystine in blood and urine.

Classic homocystinuria, the most common (frequency 1:200,000), results from reduced activity of cystathionine β-synthase (Fig. 434e-1), the pyridoxal phosphate–dependent enzyme that condenses homocysteine with serine to form cystathionine. Most patients present between