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431 Inherited Disorders of Amino Acid Metabolism in Adults

ethnic populations, but clinical symptoms are remarkably similar, and treatment guidelines apply to all. Symptomatic treatment is available for these disorders, and today, advances in the field includ ing newborn screening have resulted in more definitive diagnosis and better treatment approaches. There are many promising thera pies on the horizon with several ongoing clinical trials, including those investigating the use of ERT, mRNA therapy, gene replace ment therapy, gene editing, and substrate reduction therapy. In the past, prognosis for many disorders of carbohydrate metabolism was guarded, but with early diagnosis and better management, survival rates have improved and many affected children are surviving into adulthood. ■ ■FURTHER READING Fernandes SA et al: Benign or not benign? Deep phenotyping of liver glycogen storage disease IX. Mol Genet Metab 131:299, 2020. Heinemann JB et al: Features and outcome of galactokinase defi ciency in children diagnosed by newborn screening. J Inherit Metab Dis 34:399, 2011. Hong KN et al: International consensus on differential diagnosis and management of patients with Danon disease: JACC state-of-the-art review. J Am Coll Cardiol 82:1628, 2023. Grünert SC et al: Improved inflammatory bowel disease, wound healing and normal oxidative burst under treatment with empa gliflozin in glycogen storage disease type Ib. Orphanet J Rare Dis 15:218, 2020. Hannah WB et al: Glycogen storage diseases. Nat Rev Dis Primers 9:46, 2023. Hedberg-Oldfors C et al: Cardiomyopathy as presenting sign of glycogenin-1 deficiency—report of three cases and review of the literature. J Inherit Metab Dis 40:139, 2017. Herbert M et al: Role of continuous glucose monitoring in the man agement of glycogen storage disorders. J Inherit Metab Dis 41:917, 2018. Katler QS et al: A multinational study of acute and long-term out comes of Type 1 galactosemia patients who carry the S135L (c.404C

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Inherited Disorders

of Amino Acid Metabolism

in Adults Amino acids are the building blocks of proteins and serve as neurotransmitters (glycine, glutamate, γ-aminobutyric acid) or as pre cursors of hormones, coenzymes, pigments, purines, or pyrimidines. Eight amino acids, referred to as essential (histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine), cannot be synthesized by humans and must be obtained from dietary sources. The others can be formed endogenously. Each amino acid has a unique degradative pathway by which its nitrogen and carbon com ponents are used for the synthesis of other amino acids, carbohydrates, and lipids. Disorders of amino acid metabolism and transport (Chap. 432) are individually rare—the incidences range from 1 in 10,000 for cystinuria or phenylketonuria to 1 in 200,000 for homocys tinuria or alkaptonuria—but collectively, they affect perhaps 1 in 4000 newborns. Almost all are transmitted as autosomal recessive traits. Inherited Disorders of Amino Acid Metabolism in Adults CHAPTER 431 The features of inherited disorders of amino acid catabolism are summarized in Table 431-1. 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 path ways of metabolic “runoff.” Biochemical and genetic heterogeneity are common. Six distinct forms of hyperphenylalaninemia and nine forms of homocystinuria (with or without methylmalonic acidemia) are recognized. Such heterogeneity reflects the complexity of

amino acid metabolism requiring multiple enzymes (gene products) for proper functioning. The manifestations of these conditions differ widely (Table 431-1). 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) dys function, in the form of delays in development/intellectual disability, seizures, or behavioral disturbances, is present in more than half the disorders. Protein-induced vomiting, neurologic dysfunction, and hyperammonemia occur in many disorders of the urea cycle. Metabolic ketoacidosis, often accompanied by hyperammonemia, is frequent in organic acidemias. Some disorders produce focal tissue or organ involvement such as liver disease, renal failure, cutaneous abnormali ties, or ocular lesions. Defects in the synthesis of nonessential amino acids (asparagine, glutamine, proline, serine) involve predominantly the brain with neu rologic symptoms, with other organs occasionally affected. Dominant mutations in at least one of these genes can cause tremor or spastic paraplegia in adults. The analysis of plasma amino acids (by ion-exchange chromatog raphy or liquid chromatography/tandem mass spectrometry), 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, more commonly, by DNA testing. The clinical manifestations in many of these conditions can be prevented or mitigated if a diagno sis 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 iden tify 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

TABLE 431-1 Inherited Disorders of Amino Acid Metabolism AMINO ACID(S) CONDITION ENZYME DEFECT CLINICAL FINDINGS INHERITANCE Phenylalanine Phenylketonuria Phenylalanine hydroxylase Intellectual disability, microcephaly, hypopigmented skin and hairs, eczema, “mousy” odor DHPR deficiency Dihydropteridine reductase Intellectual disability, hypotonia, spasticity, myoclonus AR PTPS deficiency 6-Pyruvoyl-tetrahydropterin synthase Dystonia, neurologic deterioration, seizures, intellectual disability GTP cyclohydrolase 1 deficiency GTP cyclohydrolase 1 Intellectual disability, seizures, dystonia, temperature instability Carbinolamine dehydratase deficiency Pterin-4α-carbinolamine dehydratase Transient hyperphenylalaninemia (benign) AR PART 12 Endocrinology and Metabolism DNAJC12 deficiency Hydroxylase co-chaperone Dystonia, parkinsonism, intellectual disability AR Tyrosine Tyrosinemia type 1 (hepatorenal) Fumarylacetoacetate hydrolase Liver failure, cirrhosis, rickets, failure to thrive, peripheral neuropathy, “boiled cabbage” odor Tyrosinemia type 2 (oculocutaneous) Tyrosine transaminase Palmoplantar keratosis, painful corneal erosions with photophobia, learning disability Tyrosinemia type 3 4-Hydroxyphenylpyruvate dioxygenase Hypertyrosinemia with normal liver function, occasional mental delay Hawkinsinuria 4-Hydroxyphenylpyruvate dioxygenase Transient failure to thrive, metabolic acidosis in infancy AD Alkaptonuria Homogentisic acid oxidase Ochronosis, arthritis, cardiac valve involvement, coronary artery calcification Maleylacetoacetate isomerase deficiency Maleylacetoacetate isomerase No clinical symptoms, elevated succinylacetone in blood and urine Albinism (oculocutaneous) Tyrosinase Hypopigmentation of hair, skin, and optic fundus; visual loss; photophobia Albinism (ocular) Different enzymes or transporters Hypopigmentation of optic fundus, visual loss AR, XL DOPA-responsive dystonia Tyrosine hydroxylase Rigidity, truncal hypotonia, tremor, intellectual disability AR GABA 4-Hydroxybutyric aciduria Succinic semialdehyde dehydrogenase Seizures, intellectual disability, hypotonia AR ABAT deficiency GABA transaminase

Seizures, intellectual disability, hypotonia AR Tryptophan Hydroxykynureninuria Kynureninase Intellectual disability, spasticity AR Histidine Histidinemia Histidine-ammonia lyase Benign AR Urocanic aciduria Urocanase Occasional intellectual disability AR Formiminoglutamic aciduria Formiminotransferase Occasional intellectual disability AR Glycine Glycine encephalopathy Glycine cleavage (4 enzymes) Infantile seizures, lethargy, apnea, profound intellectual disability Sarcosinemia Sarcosine dehydrogenase Benign AR Hyperoxaluria type I Alanine:glyoxylate aminotransferase Calcium oxalate nephrolithiasis, renal failure AR Hyperoxaluria type II D-Glyceric acid dehydrogenase/ glyoxylate reductase Serine 3-PGDH deficiency Phosphoglycerate dehydrogenase Seizures, microcephaly, intellectual disability AR PSAT1 deficiency Phosphoserine aminotransferase Seizures, microcephaly, intellectual disability AR PSP deficiency Phosphoserine phosphatase Seizures, microcephaly, intellectual disability AR Proline Hyperprolinemia type 1 Proline oxidase Benign AR Hyperprolinemia type 2 Δ1-Pyrroline-5-carboxylate dehydrogenase Hyperhydroxyprolinemia Hydroxyproline oxidase Benign AR Prolidase deficiency Prolidase Mild intellectual disability, chronic dermatitis, autoimmunity AR PYCR1 deficiency Pyrroline-5-carboxylate reductase 1 Wrinkly skin, joint laxity, typical facial features, intellectual disability, osteopenia, intrauterine growth retardation, hypotonia PYCR2 deficiency Pyrroline-5-carboxylate reductase 2 Microcephaly, hypomyelination, and reduced cerebral white matter volume, failure to thrive, intellectual disability, movement disorders, seizures Proline (ornithine, arginine, citrulline) Δ1-Pyrroline-5-carboxylate synthase deficiency Δ1-Pyrroline-5-carboxylate synthase Hypotonia, seizures, neurodegeneration, peripheral neuropathy, joint laxity, skin hyperelasticity, subcapsular cataracts, hyperammonemia, adult spastic paraparesis (AD) Methionine Hypermethioninemia Methionine adenosyltransferase Usually benign AR S-Adenosylhomocysteine hydrolase deficiency S-Adenosylhomocysteine hydrolase Hypotonia, intellectual disability, absent tendon reflexes, delayed myelination Glycine N-methyltransferase deficiency Glycine N-methyltransferase Elevated liver transaminases AR Adenosine kinase deficiency Adenosine kinase Intellectual disability, seizures, liver dysfunction AR

AR AR AR AR AR AR AR AR AR AR Calcium oxalate nephrolithiasis, renal failure AR Febrile seizures, intellectual disability AR AR AR AR, AD AR (Continued)

TABLE 431-1 Inherited Disorders of Amino Acid Metabolism (Continued) AMINO ACID(S) CONDITION ENZYME DEFECT CLINICAL FINDINGS INHERITANCE Homocysteine Homocystinuria Cystathionine β-synthase Lens dislocation, thrombotic vascular disease, intellectual disability, osteoporosis Homocystinuria 5,10-Methylenetetrahydrofolate reductase Homocystinuria Methionine synthase and Methionine synthase reductase (cblE, G) Homocystinuria and methylmalonic acidemia Vitamin B12 lysosomal efflux and metabolism (cblC, -epiC, -D, -F, -J, -X) Cystathionine Cystathioninuria β-Cystathioninase Benign AR Cysteine Sulfocystinuria Sulfite oxidase or molybdenum cofactor deficiency Lysine Hyperlysinemia, saccharopinuria α-Aminoadipic semialdehyde synthase Benign AR Pyridoxine-dependent seizures L-Δ1-Piperideine-6-carboxilate dehydrogenase Lysine, tryptophan α-Ketoadipic acidemia α-Ketoadipic acid dehydrogenase DHTKD1 Lysine, tryptophan Glutaric acidemia type 1 Glutaryl-CoA dehydrogenase Progressive severe dystonia and athetosis, motor delays AR Ornithine Gyrate atrophy of the choroid and retina Ornithine-Δ-aminotransferase Myopia, night blindness, loss of peripheral vision, cataracts, chorioretinal degeneration Urea cycle Carbamoylphosphate synthase-1 deficiency Carbamoylphosphate synthase-1 Lethargy progressing to coma, protein aversion, intellectual disability, hyperammonemia N-Acetylglutamate synthase deficiency N-Acetylglutamate synthase Lethargy progressing to coma, protein aversion, intellectual

disability, hyperammonemia Ornithine transcarbamylase deficiency Ornithine transcarbamylase Lethargy progressing to coma, protein aversion, intellectual disability, hyperammonemia Citrullinemia type 1 Argininosuccinate synthase Lethargy progressing to coma, protein aversion, intellectual disability, hyperammonemia, liver failure Argininosuccinic acidemia Argininosuccinate lyase Lethargy progressing to coma, protein aversion, intellectual disability, hyperammonemia, trichorrhexis nodosa, liver failure Arginase deficiency Arginase Spastic tetraparesis, microcephaly, intellectual disability, mild hyperammonemia Hyperornithinemia, hyperammonemia, homocitrullinuria Mitochondrial ornithine carrier ORNT1 Vomiting, lethargy, failure to thrive, intellectual disability, episodic confusion, hyperammonemia, protein intolerance Citrullinemia type 2 Mitochondrial aspartate/glutamate carrier CTLN2 Glutamine Glutamine synthetase deficiency Glutamine synthase Brain malformations, pachygyria, seizures, hypotonia, intellectual disability, dysmorphic features, low glutamine Glutaminase deficiency Glutaminase Epileptic encephalopathy, intellectual disability, ataxia, elevated glutamine Asparagine Asparagine synthetase deficiency Asparagine synthase Epileptic encephalopathy, seizures, microcephaly, simplified gyration pattern, hypotonia, tetraplegia, intellectual disability Valine Isobutyryl-CoA dehydrogenase deficiency Isobutyryl-CoA dehydrogenase Benign AR Isoleucine, leucine, valine Maple syrup urine disease Branched chain ketoacid dehydrogenase (E1α, E1β, E2,

E3 deficiency) Isoleucine, leucine, valine Hypervalinemia Branched-chain amino acid transferase 2 (BCAT2) Isoleucine, leucine, valine Branched-chain amino acid deficiency Branched chain ketoacid dehydrogenase kinase (BCHDK) Leucine Isovaleric acidemia Isovaleryl-CoA dehydrogenase Acidosis, ketosis, vomiting, coma, hyperammonemia, “sweaty feet” odor, protein intolerance 3-Methylcrotonyl

glycinuria 3-Methylcrotonyl-CoA carboxylase Stress-induced metabolic acidosis, hypotonia, hypoglycemia, “cat’s urine” odor 3-Methylglutaconic aciduria type I 3-Methylglutaconyl-CoA hydratase deficiency 3-Hydroxy-3-methylglutaric aciduria 3-Hydroxy-3-methylglutaryl-CoA lyase Stress-induced hypoketotic hypoglycemia and acidosis, encephalopathy, hyperammonemia

AR Intellectual disability, gait and psychiatric abnormalities, recurrent strokes AR Intellectual disability, hypotonia, seizures, megaloblastic anemia AR Intellectual disability, lethargy, failure to thrive, hypotonia, seizures, megaloblastic anemia AR, XL Inherited Disorders of Amino Acid Metabolism in Adults
CHAPTER 431 Seizures, intellectual disability, dislocated lenses AR Seizures, intellectual disability AR Benign AR AR AR AR XL AR AR AR AR Neonatal intrahepatic cholestasis, adult presentation with sudden behavioral changes and stupor, coma, hyperammonemia, liver failure AR AR AR Lethargy, vomiting, encephalopathy, seizures, intellectual disability, “maple syrup” odor, protein intolerance AR Autism, headaches, intellectual disability AR Autism, epilepsy, intellectual disability, microcephaly AR AR Stress-induced acidosis, leukodystrophy, hypotonia, hepatomegaly AR AR (Continued)

TABLE 431-1 Inherited Disorders of Amino Acid Metabolism (Continued) AMINO ACID(S) CONDITION ENZYME DEFECT CLINICAL FINDINGS INHERITANCE Isoleucine 2-Methylbutyryl-glycinuria 2-Methylbutyryl-CoA dehydrogenase Benign AR 2-Methyl-3-hydroxybutyrylCoA dehydrogenase deficiency 2-Methyl-3-hydroxybutyryl-CoA dehydrogenase 3-Oxothiolase deficiency 3-Oxothiolase Fasting-induced acidosis and ketosis, vomiting, lethargy AR Isoleucine, methionine, threonine,

valine Propionic acidemia (pccA, -B) Propionyl-CoA carboxylase Metabolic ketoacidosis, hyperammonemia, hypotonia, lethargy, coma, protein intolerance, intellectual disability, hyperglycinemia Multiple carboxylase/ biotinidase deficiency Holocarboxylase synthase or biotinidase PART 12 Endocrinology and Metabolism Methylmalonic acidemia (mutase, cblA, B, racemase) Methylmalonyl-CoA mutase/ racemase or cobalamin reductase/ adenosyltransferase Abbreviations: AD, autosomal dominant; AR, autosomal recessive; Cbl, cobalamin; DOPA, dihydroxyphenylalanine; GABA, γ-aminobutyric acid; GTP, guanosine 5′-triphosphate; XL, X-linked. cases should be referred to a metabolic center for initiation of therapy. The parents need to be counseled about the natural history of the disease and its recurrence risk in future pregnancies. In some cases, parents need testing because they might have a disorder themselves (such as glutaric acidemia type 1, methylcrotonyl coenzyme A carbox ylase deficiency, primary carnitine deficiency, or fatty acid oxidation defects) since mothers with these conditions can sometimes be identi fied by abnormal newborn screening results in their offspring. Some metabolic disorders can remain asymptomatic until adult age, present ing only when fasting or severe stress requires 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 431-1) result from impaired conversion of phenylalanine to tyrosine. The most common and clinically important is phenylketonuria (frequency 1:16,500), which is an autosomal recessive disorder characterized by an increased con centration of phenylalanine and its by-products in body fluids and by severe intellectual disability 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 norepi nephrine and serotonin. Phenylalanine is a competitive inhibitor of tyrosinase, a key enzyme in the pathway of melanin synthesis, resulting in hypopigmentation of hair and skin. Untreated children with classic phenylketonuria are normal at birth but fail to attain early develop mental milestones, develop microcephaly, and demonstrate progressive impairment of cerebral function. Hyperactivity, seizures, and severe intellectual disability are major clinical problems later in life. Elec troencephalographic abnormalities; “mousy” odor of skin, hair, and urine (due to phenylacetate accumulation); and a tendency to develop hypopigmentation (compared to the family background) 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, newborns in North America, Australia, and Europe are screened by determinations of blood phe nylalanine 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. Treatment consists of a special diet low in phenylalanine and

Developmental regression, seizures, and rigidity sometimes triggered by illnesses XL AR Metabolic ketoacidosis, diffuse rash, alopecia, seizures, intellectual disability AR Metabolic ketoacidosis, hyperammonemia, hypertonia, lethargy, coma, protein intolerance, intellectual disability, hyperglycinemia AR supplemented with tyrosine since tyrosine becomes an essential amino acid in phenylalanine hydroxylase deficiency. With ther apy, plasma phenylalanine concentrations should be maintained between 120 and 360 μmol/L for life. Compliance with the strict diet is often difficult

as patients become older; increased levels of phenylalanine in adults can cause deficits in executive function or psychiatric symptoms. Oral tetrahydrobiopterin (5–20 mg/kg per d), an essential cofactor of phenylalanine hydroxylase, can reduce phenylalanine levels in some patients with phenylketonuria in conjunction with a low-protein diet. Pegvaliase is a pegylated form of phenylalanine ammonia lyase, a bacterial enzyme that converts phenylalanine to trans-cinnamic acid and ammonia. This inject able drug can substantially reduce phenylalanine levels, allowing a normal diet. The bacterial origin of pegvaliase can cause immune reactions that limit its use in some patients with phenylketonuria. Women with phenylketonuria can become pregnant. If mater nal phenylalanine levels are not strictly controlled before and dur ing pregnancy, their offspring are at increased risk for congenital defects and microcephaly (maternal phenylketonuria). After birth, these children have severe intellectual disability and growth retar dation. 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 include 10 biochemically and clinically distinct disorders (Table 431-1) characterized by increased concentration of the sulfur-containing amino acid homocysteine in blood and urine. Classic homocystinuria, the most common (frequency 1:450,000), results from reduced activity of cystathionine β-synthase (Fig. 431-1), the pyridoxal phosphate–dependent enzyme that condenses homocys teine with serine to form cystathionine. Most patients present between 3 and 5 years of age with dislocated optic lenses and intellectual disabil ity (in about half of cases). Some patients develop a marfanoid habitus and radiologic evidence of osteoporosis. Life-threatening vascular complications (affecting coronary, renal, and cerebral arteries) can occur during the first decade of life and are the major cause of morbidity and mortality. Classic homocystin uria can be diagnosed with analysis of plasma amino acids, showing elevated methionine and presence of free homocystine. Total plasma homocysteine is also extremely elevated (usually >100 μM). Elevated levels of methionine can be also detected by neonatal screening, but milder variants can be missed by this approach. Treatment consists of a special diet restricted in protein and methionine. In approximately half of patients, oral pyridoxine (25–500 mg/d) produces a fall in plasma methionine and homocysteine concentration in body fluids. Folate and vitamin B12 deficiency should be prevented by adequate supplementa tion. Betaine is also effective in reducing homocysteine levels by favor ing its remethylation to methionine.

Re-methylation Methionine Synthase Reductase (cblE) CH3-S-(CH2)2-CH-COOH Glycine Serine Methionine Synthase (cblG) Methionine TetraHydro Folate (THF) Cobalamin (B12) cbl C, D, F, J, X, epi-cblC Dimethylglycine Betaine Homocysteine Methyltransferase Methyl-Cobalamin 5,10-Methylene THF N5-Methyl THF Methylene Tetrahydro Folate Reductase (MTHFR) Cystathionine b Synthase (B6) Cystathionase (B6) `-Ketobutyrate Cysteine FIGURE 431-1 Pathways, enzymes, and coenzymes involved in the homocystinurias. Methionine transfers a methyl group during its conversion to homocysteine. Defects in methyl transfer or in the subsequent metabolism of homocysteine by the pyridoxal phosphate (vitamin B6)-dependent cystathionine β-synthase increase plasma methionine levels. Homocysteine is transformed into methionine via remethylation. This occurs through methionine synthase, a reaction requiring methylcobalamin and folic acid. Deficiencies in these enzymes or lack of cofactors is associated with decreased or normal methionine levels. In an alternative pathway, homocysteine can be remethylated by betaine:homocysteine methyl transferase. The other forms of homocystinuria are the result of impaired remethylation of homocysteine to methionine. This can be caused by defective

methionine synthase or reduced availability of two essential cofactors, 5-methyltetrahydrofolate and methylcobalamin (methylvitamin B12). In contrast to cystathionine β-synthase, elevated levels of free homocysteine are associated with low levels of methionine in the plasma amino acid profile in remethylation defects. Most of these conditions present with delays in development and some with megaloblastic anemia (methionine synthase-cblG and methio nine synthase reductase-cblE deficiency, in addition to combined methylmalonic acidemia-homocystinuria- cblC, cblD, cblF, cblJ, see Chap. 104). Therapy in these cases requires administration of meth ylfolate, hydroxycobalamin (an activated form of vitamin B12), and betaine. Hyperhomocysteinemia refers to increased total plasma concentra tion of homocysteine with or without an increase in free homocys teine (disulfide form). Hyperhomocysteinemia, in the absence of significant homocystinuria, is found in some heterozygotes for the genetic defects noted above or in homozygotes for milder variants. Changes of homocysteine levels are also observed with deficiency of pyridoxine, folic acid, or vitamin B12; with increasing age; with smoking; in postmenopausal women; in patients with renal failure, hypothyroidism, leukemias, autoinflammatory disorders; and during therapy with drugs such as methotrexate, nitrous oxide, givosiran, isoniazid, and some antiepileptic agents. Elevated homocysteine pro duces endothelial dysfunction, acting as an atherogenic and thrombo philic agent. Increased total plasma homocysteine has been associated with an increased risk for coronary, cerebrovascular, and peripheral arterial disease as well as for deep-vein thrombosis. In addition, hyperhomocysteinemia and folate and vitamin B12 deficiencies have been associated with an increased risk of neural tube defects in preg nant women and dementia (Alzheimer’s type), as well as Parkinson’s disease in the general population. Vitamin B12, folic acids, and pyri doxine supplements can reduce total plasma homocysteine levels in these cases, with reduction of the risk of stroke when levels are more severely increased (>30 μM).

Methyl transfer NH2 ATP Methionine Adenosyl Transferase (MAT) N-Methylglycine (Sarcosine) S-Adenosyl Methionine Inherited Disorders of Amino Acid Metabolism in Adults
CHAPTER 431 Glycine N-Methyltransferase Methyltransferases CH3 S-Adenosyl Homocysteine Glycine Betaine S-Adenosyl Homocysteine Hydrolase Creatine Guanidinoacetate Methyltransferase Homocysteine Adenosine Serine Guanidinoacetate Cystathionine Trans-sulfuration ALKAPTONURIA
Alkaptonuria is a rare (frequency 1:250,000) disorder of tyrosine catabolism in which deficiency of homogentisate 1,2-dioxygenase (also known as homogentisic acid oxidase) leads to excretion of large amounts of homogentisic acid in urine and accumulation of oxidized homogentisic acid pigment in connective tissues (ochronosis). Alkap tonuria may go unrecognized until middle life, when degenerative joint disease develops. Prior to this time, about half of patients might be diagnosed for the presence of urine that becomes dark with stand ing or addition of alkali. Foci of gray-brown scleral pigment and gen eralized darkening of the concha, antihelix, and, finally, helix of the ear usually develop after age 30. Low back pain usually starts between 30 and 40 years of age. Ochronotic arthritis is heralded by pain, stiff ness, and some limitation of motion of the hips, knees, and shoulders. Acute arthritis may resemble rheumatoid arthritis, but small joints are usually spared. Pigmentation of heart valves, larynx, tympanic membranes, and skin occurs, and occasional patients develop pig mented renal or prostatic calculi. Pigment deposition in the heart and blood vessels leads to aortic stenosis necessitating valve replacement, especially after 60 years of age. The diagnosis should be suspected in a patient whose urine darkens to blackness. Homogentisic acid in urine is identified by urine organic acid analysis. Ochronotic arthritis is treated symptomatically with pain medications, spinal surgery, and arthroplasty (Chap. 383). Nitisinone (2-[2-nitro4-trifluoromethylbenzoyl]-1,3-cyclohexanedione), a drug used in tyrosinemia type 1, at low

dose (10 mg/d) reduces urinary excre tion of homogentisic acid, delays progression, and improves clini cal signs of alkaptonuria. UREA CYCLE DEFECTS Excess ammonia generated from protein nitrogen is removed by the urea cycle, a process mediated by several enzymes and transporters (Fig. 431-2, Table 431-1). Complete absence of any of these enzymes usually causes severe hyperammonemia in newborns, while milder variants can be seen in adults. The accumulation of ammonia and glu tamine leads to direct neuronal toxicity and brain edema. Deficiencies

Acetyl-CoA+Glutamate NAG Synthase N-acetyl-Glutamate CO2+H2O CPS-1 CA5A H2CO3+NH3+2ATP Carbamylphosphate + Ornithine Mitochondrion PART 12 Endocrinology and Metabolism Aspartate Cytosol Citrin ORNT1 Aspartate + ASA Synthase Argininosuccinic Acid Arginine FIGURE 431-2 The urea cycle. This cycle, which is fully expressed only in the liver, forms urea starting from ammonia (NH3) derived from the nitrogen group of all amino acids. It requires many enzymes and mitochondrial transporters, any of which can be defective and may impair the function of the urea cycle. Ammonia escaping the urea cycle in periportal hepatocytes is conjugated with glutamate by glutamine synthase in perivenous hepatocytes to generate glutamine. ARG, arginase; ASA, argininosuccinic acid; ASL, argininosuccinate lyase; ASS, argininosuccinate synthase; CA5A, carbonic anhydrase 5a; citrin (SLC25A13), aspartate/glutamate exchanger; CP, carbamylphosphate; CPS-1, carbamylphosphate synthase 1; CTP, cytidine triphosphate; HHH, hyperammonemia, hyperornithinemia, homocitrullinuria syndrome; NAG, N-acetylglutamate; NAGS, N-acetylglutamate synthase; ORNT1 (SLC25A15), ornithine/citrulline mitochondrial transporter; OTC, ornithine transcarbamylase; UTP, uridine triphosphate. in urea cycle enzymes are individually rare, but as a group, they affect ~1:35,000 individuals. They are all transmitted as autosomal recessive traits, with the exception of ornithine transcarbamylase deficiency, which is X-linked and the most frequent urea cycle defect. Hepatocytes of females with ornithine transcarbamylase deficiency express either the normal or the mutant allele due to random X-inactivation and may be unable to remove excess ammonia if mutant cells are predominant. Infants with classic urea cycle defects present at 1–4 days of life with refusal to eat and lethargy progressing to coma and death. Milder enzyme deficiencies present with protein avoidance, recurrent vomiting, migraine, mood swings, chronic fatigue, irritability, and disorientation that can progress to coma. Some cases have presented with acute or chronic hepatic dysfunction. Females with ornithine transcarbamylase deficiency can present at time of childbirth due to the combination of involuntary fasting and stress that favors catabo lism. Administration of systemic corticosteroids or chemotherapy can precipitate hyperammonemia and can be fatal in previously asymp tomatic individuals of any age. These patients may be misdiagnosed as having gastrointestinal disorders, food allergies, behavioral prob lems, or nonspecific hepatitis. The diagnosis requires measurement of plasma ammonia, plasma amino acids, and urine orotic acid, useful for differentiating ornithine transcarbamylase deficiency from carba myl phosphate synthase-1 and N-acetylglutamate synthase deficiency. Increased plasma glutamine is seen with all urea cycle defects since ammonia not removed by the urea cycle in periportal hepatocytes is conjugated to glutamate by glutamine synthase in perivenous hepa tocytes. Citrulline is low or undetectable in proximal defects of the urea cycle (N-acetylglutamate synthase, carbamylphosphate synthase 1, and ornithine transcarbamylase deficiency), with urine orotic acid being increased only in ornithine transcarbamylase deficiency. Plasma citrulline is markedly increased in argininosuccinic acid synthase deficiency (citrullinemia type 1), with a milder elevation in arginino succinic acid lyase deficiency in the presence of argininosuccinic acid (argininosuccinic aciduria). Arginine levels are usually normal to low in these conditions and become markedly

elevated only in patients with arginase deficiency. In addition to urea cycle defects, hyperammonemia can also be caused by liver disease from any cause and several organic acidemias and fatty acid oxidation defects (the latter two excluded by the analysis of urine organic acids and plasma acylcarnitine profile).

Urea Cycle UTP CTP Orotic Acid NAGS Carbamyl Phosphate Ornithine OTC ORNT1 (HHH) Citrulline Urea Arginase ARG Citrulline ASS ASA Lyase ASL Fumarate TREATMENT Urea Cycle Defects Therapy is aimed at stopping catabolism and ammonia produc tion by providing adequate calories (as IV glucose and lipids in the comatose patient) and, if needed, insulin. Excess nitrogen is removed by IV phenylacetate and benzoate (0.25 g/kg for the prim ing dose and subsequently as an infusion over 24 h) that conjugate with glutamine and glycine, respectively, to form phenylacetyl glutamine and hippuric acid, water-soluble molecules efficiently excreted in urine. Arginine (200 mg/kg per d) becomes an essential amino acid (except in arginase deficiency) and should be provided intravenously to resume protein synthesis. If these measures fail to reduce ammonia, hemodialysis should be initiated promptly. Chronic therapy consists of a protein-restricted diet, phenylbutyr ate, glycerol phenylbutyrate (a liquid drug better tolerated by most patients), arginine, or citrulline supplements, depending on the specific diagnosis. Oral carglumic acid can restore a functional urea cycle in patients with N-acetylglutamate synthase deficiency and renders other therapies unnecessary. Liver transplantation should be considered in patients with severe urea cycle defects that are dif ficult to control medically. Hyperammonemia due to a functional deficiency of glutamine synthase can occur in patients receiving chemotherapy for differ ent malignancies or undergoing solid organ transplants. It can also be seen with hepatic cirrhosis. Several of these patients have been successfully rescued from hyperammonemia using the protocol described above for urea cycle defects. ■ ■FURTHER READING Guéant JL et al: Hyperhomocysteinemia in cardiovascular diseases: Revisiting observational studies and clinical trials. Thromb Haemost 123:270, 2023. Ranganath LR et al: Efficacy and safety of once-daily nitisinone for patients with alkaptonuria (SONIA 2): An international, multicentre, open-label, randomised controlled trial. Lancet Diabetes Endocrinol 8:762, 2020. Van Spronsen FJ et al: Phenylketonuria. Nat Rev Dis Primers 7:36, 2021.

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