50 - 432 Inherited Defects of Membrane Transport

432 Inherited Defects of Membrane Transport

Nicola Longo

Inherited Defects of

Membrane Transport Membrane transporters mediate the passage of amino acids, oligopeptides, sugars, cations, anions, vitamins, water, and other molecules across cellular membranes and are encoded by members of the solute-carrier gene (SLC) superfamily. These transporters are located on the plasma membrane or intracellular organelles, and their cellular and tissue distribution in addi tion to the presence (or absence) of redundant transporters explains organ involvement and possible metabolic disturbances. Transport processes are essential for the normal function of every organ, but especially the brain and sensory organs (Table 432-1). Inherited defects impairing the transport of selected amino acids that can present in adults are discussed here as examples of the abnormalities encountered; others are considered elsewhere in this text. ■ ■CYSTINURIA Cystinuria (worldwide frequency of 1 in 7000) is an autosomal reces sive disorder caused by defective transporters in the apical brush border of proximal renal tubule and small intestinal cells. It is char acterized by impaired reabsorption and excessive urinary excretion of the amino acids lysine, arginine, ornithine, and cystine that are dibasic in the physiologically acidic pH of urine. Because cystine is poorly soluble, its excess predisposes to the formation of renal, ureteral, and bladder stones. Such stones are responsible for the signs and symptoms of the disorder. There are two variants of cystinuria. Homozygotes for both variants have high urinary excretion of cystine, lysine, arginine, and ornithine. Type A heterozygotes usually have normal urinary amino acid excre tion, whereas most type B heterozygotes have moderately increased urinary excretion of cystine that, in some circumstances, can result in the formation of kidney stones. The gene for type A cystinuria (SLC3A1, chromosome 2p16.3) encodes a membrane glycoprotein. Type B cystinuria is caused by mutations in SLC7A9 (chromosome 19q13) that encodes the b0,+ amino acid transporter. The glycoprotein encoded by SLC3A1 favors the correct processing of the b0,+ membrane transporter and explains why mutations in two different genes cause a similar disease. Cystine stones account for 1–2% of all urinary tract calculi and for ~4–5% of stones in children. Cystinuria homozygotes regularly excrete 2400–7200 µmol (600–1800 mg) of cystine daily. Since the maximum solubility of cystine in the physiologic urinary pH range of 4.5–7.0 is ~1200 µmol/L

(300 mg/L), cystine needs to be diluted to 2.5–7 L of water to prevent crystalluria. Stone formation usually manifests in the second or third decade but may occur in the first year of life. Symptoms and signs are those typical of urolithiasis: hematuria, flank pain, renal colic, obstructive uropathy, and infection (Chap. 330). Recurrent uro lithiasis may lead to progressive renal insufficiency. Cystinuria is suspected after observing typical hexagonal crystals in the sediment of acidified, concentrated, chilled urine or after per forming a urinary nitroprusside test. Quantitative urine amino acid analysis shows selective overexcretion of cystine, lysine, arginine, and ornithine. Quantitative measurements are important for differentiating heterozygotes from homozygotes and for following free cystine excre tion during therapy. Management is aimed at preventing cystine crystal formation by increasing urinary volume and by maintaining an alkaline urine pH. Fluid ingestion in excess of 4 L/d is essential, and 5–7 L/d is optimal. Urinary cystine concentration should be <1000 μmol/L (250 mg/L). The daily fluid ingestion necessary to maintain this dilution of excreted cystine should be spaced over 24 h, with one-third of the total vol ume ingested between bedtime and 3 a.m. Cystine solubility rises sharply above pH 7.5, and urinary alkalinization (with potassium citrate) can be therapeutic. Penicillamine (1–3 g/d) and tiopronin

(α-mercaptopropionylglycine, 800–1200 mg/d in four divided doses) undergo sulfhydryl-disulfide exchange with cystine to form mixed disulfides. Because these disulfides are much more soluble than cys tine, pharmacologic therapy can prevent and promote dissolution of calculi. Penicillamine can have significant side effects and should be reserved for patients who fail to respond to hydration alone or who are in a high-risk category (e.g., one remaining kidney, renal insuf ficiency). When medical management fails, shock wave lithotripsy, ureteroscopy, and percutaneous nephrolithotomy are effective for most stones. Open urologic surgery is considered only for complex staghorn stones or when the patient has concomitant renal or ureteral abnormalities. Occasional patients progress to renal failure and require kidney transplantation.

Inherited Defects of Membrane Transport CHAPTER 432 ■ ■LYSINURIC PROTEIN INTOLERANCE Lysinuric protein intolerance is characterized by a defect in renal tubular reabsorption and intestinal transport of the three dibasic amino acids lysine, arginine, and ornithine but not cystine. It is most common in Finland (1 in 60,000), southern Italy, and Japan, but is rare elsewhere. The transport defect affects basolateral rather than luminal membrane transport and causes secondary impairment of the urea cycle. The defective gene (SLC7A7, chromosome 14q11.2) encodes the y+LAT membrane transporter, which associates with the cell-surface glycoprotein 4F2 heavy chain to form the complete sodium-independent transporter y+L. Manifestations are related to impairment of the urea cycle and to immune dysfunction likely attributable to nitric oxide overproduc tion secondary to arginine intracellular trapping within white blood cells. Affected patients present in childhood with hepatosplenomegaly, protein intolerance, and episodic ammonia intoxication. Adults may present with severe osteoporosis, pancreatitis, impaired renal function, pulmonary alveolar proteinosis, various autoimmune disorders, and an incompletely characterized immune deficiency. Plasma concentra tions of lysine, arginine, and ornithine are reduced, whereas urinary excretion of lysine, arginine, ornithine, and orotic acid is increased. Hyperammonemia may develop after the ingestion of protein loads or with infections, probably because of insufficient amounts of ornithine to maintain proper function of the urea cycle. Diagnosis is confirmed by sequencing of the SLC7A7 gene that is included in most hyper ammonemia panels. Therapy consists of dietary protein restriction, supplementation of citrulline (2–8 g/d), a neutral amino acid that fuels the urea cycle when metabolized to arginine and ornithine, and nitrogen scavengers

(phenylbutyrate, benzoate) in case of persistent hyperammonemia. Pulmonary disease can respond to glucocorticoids or recombinant human granulocyte-macrophage colony-stimulating factor but might require broncho-alveolar or whole lung lavage in some patients. Women with lysinuric protein intolerance who become preg nant have an increased risk of anemia, toxemia, and bleeding complica tions during delivery. These can be minimized by aggressive nutritional therapy and control of blood pressure. Their infants can have intrauter ine growth restriction but have normal neurologic function. ■ ■CITRULLINEMIA TYPE 2 (CITRIN DEFICIENCY) Citrullinemia type 2 is a recessive condition caused by deficiency of the mitochondrial aspartate-glutamate carrier AGC2 (citrin). A defect in this transporter reduces the availability of cytoplasmic aspartate to combine with citrulline to form argininosuccinate (see Fig. 431-2), impairing the urea cycle and decreasing the transfer of reducing equivalents from the cytosol to the mitochondria through the malateaspartate NADH shuttle. Mutations in the SLC25A13 gene on chromo some 7q21.3 that encodes for this transporter are rare in Caucasians but affect ~1:20,000 people with ancestry from Japan, China, and Southeast Asia with variable penetrance. The disease can present in children with neonatal intrahepatic cho lestasis, failure to thrive, and dyslipidemia but usually presents with sudden onset between 20 and 50 years of age with recurring episodes of hyperammonemia with associated neuropsychiatric symptoms such as altered mental status, irritability, seizures, or coma-resembling hepatic encephalopathy. Some patients might come to medical attention for

TABLE 432-1 Genetic Disorders of Amino Acid Transport TISSUES MANIFESTING TRANSPORT DEFECT MOLECULAR DEFECT MAJOR CLINICAL MANIFESTATIONS INHERITANCE DISORDER SUBSTRATES Cystinuria Cystine, lysine, arginine, ornithine Proximal renal tubule, jejunal mucosa Lysinuric protein intolerance Lysine, arginine, ornithine Proximal renal tubule, jejunal mucosa Hartnup disease Neutral amino acids Proximal renal tubule, jejunal mucosa Histidinuria Histidine Proximal renal tubule, jejunal mucosa PART 12 Endocrinology and Metabolism Iminoglycinuria Glycine, proline, hydroxyproline Proximal renal tubule, jejunal mucosa Dicarboxylic aminoaciduria Glutamic acid, aspartic acid Proximal renal tubule, jejunal mucosa Hyperargininemia Arginine, lysine, ornithine Ubiquitous CAT2 cationic amino acid transporter SLC7A2 Brain branched-chain amino acid deficiency Leucine, isoleucine, valine Plasma membrane of blood-brain barrier Citrullinemia type 2 Aspartate, glutamate, malate Inner mitochondrial membrane Hyperornithinemia, hyperammonemia, homocitrullinuria Ornithine, citrulline Inner mitochondrial membrane Epileptic encephalopathy Aspartate, glutamate, malate Inner mitochondrial membrane Epileptic encephalopathy Glutamate Inner mitochondrial membrane Epileptic encephalopathy Glutamic acid, aspartic acid Presynaptic glutamatergic nerve endings Episodic ataxia Glutamic acid, aspartic acid Presynaptic glutamatergic nerve endings Brain serine deficiency Alanine, serine, cysteine, threonine Neuronal cells ASCT neutral amino acid transporter SLC1A4 Glycine encephalopathy with normal serum glycine Glycine Astrocytes and neuronal cells Hyperekplexia-3 Glycine Neuronal cells GLYT2 Presynaptic glycine transporter SLC6A5 Intellectual disability Proline, glycine, leucine, and alanine, glutamine Neuronal cells synaptic vesicles Deafness Glutamic acid Neuronal cortical synaptic vesicles Foveal hypoplasia Glutamine Retinal photoreceptors SLC38A8 Foveal hypoplasia, optic nerve decussation defects, anterior segment dysgenesis Retinitis pigmentosa Arginine, lysine, ornithine Retinal photoreceptors Cationic amino acid transporter SLC7A14 Early retinal degeneration Taurine Retinal cells TAUT taurine transporter SLC6A6 Cystinosis Cystine Lysosomal membranes Lysosomal cystine transporter Abbreviations: AD, autosomal dominant; AR, autosomal recessive. hypertriglyceridemia, pancreatitis, hepatoma, or fatty liver histo logically similar to nonalcoholic steatohepatitis. Without therapy, most symptomatic

patients die with cerebral edema within a few years. Epi sodes are usually triggered by medications (such as acetaminophen), surgery, alcohol, or high sugar intake, with the latter conditions causing NADH production in the cytoplasm. NADH is not generated by the metabolism of proteins or fats, and individuals with citrullinemia type 2 spontaneously prefer foods such as meat, eggs, and fish and avoid carbohydrates.

Shared dibasic-cystine transporter SLC3A1, SLC7A9 Cystine nephrolithiasis AR Dibasic transporter SLC7A7 Protein intolerance, hyperammonemia, intellectual disability AR Neutral amino acid transporter SLC6A19 Constant neutral aminoaciduria, intermittent symptoms of pellagra AR Histidine transporter Intellectual disability AR Shared glycine–amino acid transporter SLC6A20, SLC6A18, SLC36A2 None AR Shared dicarboxylic amino acid transporter SLC1A1 None AR Hyperargininemia, Hyperammonemia (?) AR Branched-chain amino acid transporter SLC7A5 Microcephaly, intellectual disability, seizures, autism AR Mitochondrial aspartate/ glutamate carrier 2 SLC25A13 Sudden behavioral changes with stupor, coma, hyperammonemia AR Mitochondrial ornithine carrier SLC25A15 Lethargy, failure to thrive, intellectual disability, episodic confusion, hyperammonemia, protein intolerance AR Mitochondrial aspartate/ glutamate carrier 1 SLC25A12 Intellectual disability, epilepsy, hypotonia, cerebral atrophy, and hypomyelination AR Mitochondrial glutamate carrier SLC25A22 Intellectual disability, epilepsy AR EEAT2 Neuronal dicarboxylic amino acid transporter SLC1A2 Developmental and Epileptic Encephalopathy AD EEAT1 Neuronal dicarboxylic amino acid transporter SLC1A3 Episodic ataxia AD Progressive microcephaly, intellectual disability, spasticity AR GLYT1 astrocyte glycine transporter SLC6A9 Arthrogryposis, apnea, axial hypotonia, spasticity, intellectual disability AR Exaggerated startle response, hypertonia, apnea AR NTT4 synaptic vesicle neutral amino acid transporter SLC6A17 Intellectual disability, tremor AR VGLUT3 vesicular glutamate transporter SLC17A8 Deafness AD AR Retinitis pigmentosa, blindness AR Nystagmus, vision loss, retinal degeneration AR Renal failure, hypothyroidism, blindness AR Laboratory studies during an acute attack can show elevated ammo nia, citrulline, and arginine with low or normal levels of glutamine (the latter is usually increased in classic urea cycle defects). Levels of galactose1-phosphate in red blood cells are also increased, reflecting defective transfer of reducing equivalents from the cytosol to mitochondria. The diagnosis is confirmed by demonstrating pathogenic variants in the SLC25A13 gene. Liver transplantation prevents progression of the disease and normalizes biochemical parameters. A ketogenic diet high in fats and proteins and low in carbohydrates with supplements of

medium-chain triglycerides, arginine, and pyruvate is also effective in preventing or delaying disease progression. ■ ■HARTNUP DISEASE Hartnup disease (frequency 1 in 24,000) is an autosomal recessive dis order characterized by pellagra-like skin lesions, variable neurologic manifestations, and neutral and aromatic aminoaciduria. Alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, glutamine, asparagine, and histidine are excreted in urine in quantities 5–10 times greater than normal, and intestinal transport of these same amino acids is defective. The defective neutral amino acid transporter, B°AT1 encoded by the SLC6A19 gene on chro mosome 5p15, requires either collectrin or angiotensin-converting enzyme 2 (one of the binding sites for SARS-CoV-2) for surface expres sion in the kidney and intestine, respectively. The clinical manifestations result from nutritional deficiency of the essential amino acid tryptophan, caused by its intestinal and renal malabsorption, and of niacin, which derives in part from tryptophan metabolism. Only a small fraction of patients with Hartnup disease develop symptoms, implying that manifestations depend on other factors in addition to the transport defect. The

diagnosis of Hartnup disease should be suspected in any patient with clinical features of pel lagra, recurrent diarrhea, and/or neurologic symptoms who does not have a history of dietary niacin deficiency (Chap. 345). The neurologic and psychiatric manifestations range from attacks of spastic paraplegia to cerebellar ataxia to mild emotional lability to frank delirium, and they are usually accompanied by exacerbations of the erythematous, eczematoid skin rash. Fever, sunlight, stress, and sulfonamide therapy provoke clinical relapses. Diagnosis is made by detection of the neutral aminoaciduria (which does not occur in dietary niacin deficiency) and is confirmed by genetic testing of the SLC6A19 or the CTLRN gene (coding for collectrin), whose deficiency produces a biochemical phe nocopy. Treatment includes a high-protein diet and daily nicotinamide supplementation (50–250 mg). ■ ■CYSTINOSIS Cystinosis (frequency 1 in 100,000–200,000) is an autosomal reces sive disorder caused by mutations in the CTNS gene encoding the lysosomal cystine/proton transporter (cystinosin). In this condition, cystine derived from protein degradation accumulates inside lyso somes and forms crystals due to its poor solubility. Depending on the degree of impairment of transporter function, three clinical forms are recognized. The most severe form, classic nephropathic cystinosis, causes renal Fanconi syndrome with rickets during the first year of life and, without treatment, evolves to renal failure usually by 10 years of

age. Juvenile nephropathic cystinosis presents with proteinuria slowly leading to kidney failure, whereas photophobia, caused by deposition of cystine crystals in the cornea, is the only manifestation of ocular nonnephropathic cystinosis. Cystinosis is suspected by the identifica tion of cystine crystals in the cornea by slit lamp examination and diagnosed by measuring cystine content in white blood cells and/or DNA testing (including deletion analysis) of the CTNS gene. Therapy consists in the administration of extended release cysteamine bitartrate that enters lysosomes and forms a mixed disulfide with cysteine that is exported from the lysosome using a cationic amino acid transporter. This drug is given orally and should be slowly increased to the main tenance dose of 1.3 g/m2 divided into two daily administrations while monitoring white blood cell (WBC) cystine levels for efficacy. This therapy delays renal failure and is more effective if started early in the course of the disease. Cysteamine eye drops can relieve photophobia. Renal replacement therapy with salts, alkali, and activated vitamin D is necessary for renal Fanconi syndrome. Cystine accumulation occurs in all organs and tissues, causing additional complications such as hypothyroidism, hypohydrosis, diabetes, and delayed puberty in both males and females with primary hypogonadism in males. Growth hormone replacement, l-thyroxine for hypothyroidism, insulin for diabetes mellitus, and testosterone for hypogonadism in males may be necessary. Despite therapy, many patients with cystinosis progress to end-stage renal failure and require kidney transplantation. Late-onset complications include hepatomegaly and splenomegaly that occur in approximately one-third of subjects and a vacuolar myopathy caus ing weakness (initially involving the distal extremities), swallowing difficulties, gastrointestinal dysmotility, and pulmonary insufficiency. Before the availability of cystine-depleting therapy and renal trans plantation, the life span in nephropathic cystinosis was <10 years. With current therapies, affected individuals can survive into the late forties with satisfactory quality of life.

Inherited Defects of Membrane Transport CHAPTER 432 ■ ■FURTHER READING Bölsterli BK et al: Ketogenic diet treatment of defects in the mito chondrial malate aspartate shuttle and pyruvate carrier. Nutrients 14:3605, 2022. Levtchenko E et al: Expert guidance on the multidisciplinary man agement of cystinosis in adolescent and adult patients. Clin Kidney J 15:1675, 2022. Servais A et al: Cystinuria: Clinical practice recommendation. Kidney Int 99:48, 2021. Yahyaoui R, Pérez-frías J:

Amino acid transport defects in human inherited metabolic disorders. Int J Mol Sci 21:119, 2019.

This page intentionally left blank

Revision #1
Created 2026-01-06 16:35:32 UTC by Omar Ayman
Updated 2026-01-06 16:35:32 UTC by Omar Ayman