

13.1 Introduction

■ Transport of Amino Acids

Transcellular transport mechanisms are responsible for the transport of free amino acids through epithelial cells and are mainly present in cells of the intestinal mucosa and the renal tubules. Most amino acids are transported via a sodium-dependent transport system. However, sodium-independent transport and passive diffusion exist. Transmembrane transporters may be specific for single amino acids (e.g. histidine, glycine) or for groups of amino acids (e.g. dibasic amino acids, dibasic amino acids and cystine, neutral amino acids or dicarboxylic amino acids).

A defective transporter may lead to deficient or absent absorption or reabsorption of a single amino acid or a group of amino acids, resulting in only biochemical pathology as “non-disease” or in errors of metabolism with clinical relevance [1].

■ Cystinuria

Cystinuria is the result of defective transport of cystine and the dibasic amino acids lysine, arginine and ornithine through the brush border epithelial cells of the proximal renal tubules (reabsorption) and the small intestine (absorption) [2] due to mutations in the SLC3A1 gene (former rBAT gene) on chromosome 2p21 (type I) [3–5] or on chromosome 19q13.1 (type II and III=type non-I) [6]. The mode of inheritance is autosomal recessive because heterozygotes manifest either amino aciduria (type I) or slight to moderate hyperexcretion of cystine and dibasic amino acids (type II or III) [7, 8]. According to Rosenberg [9] only type III homozygotes, but not type I and II homozygotes, show an increase in plasma cystine levels after oral cystine loading, while other authors deny the existence of a type III [10]. Homozygotes and compound heterozygotes develop urolithiasis due to the low solubility of cystine (<200–300 mg/l). The intestinal malabsorption of cystine and dibasic amino acids has no clinical relevance. Treatment has to prevent stone formation by high fluid intake during day

and night and alkalization of the urine to increase cystine solubility. Treatment with thiol-derivatives, such as D-penicillamine or α -mercapto-propionylglycine and the sulphydryl compound captopril intend to prevent or dissolve stones by forming water-soluble cysteine disulfides with cystine [11].

■ Dicarboxylic Aminoaciduria

Glutamic acid and aspartic acid secretion is highly increased due to a specific tubular defect. This transport defect seems to be related to the glutamate transporter EAAC1 on chromosome 9p24 [12]. The few patients described showed neurological (external ophthalmoplegia, deafness, peripheral polyneuropathy), mental (oligophrenia) or no symptoms [13–15]. There is no treatment.

■ Hartnup Disorder

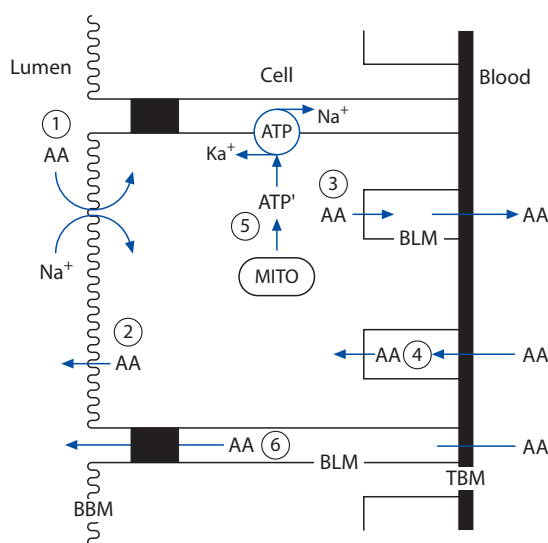
The neutral amino acids alanine, serine, threonine, asparagine, glutamine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, histidine and citrulline share a common transporter at the luminal border of the epithelial cells in the renal tubuli and the epithelial cells in the small intestine [16]. In Hartnup disorder an impairment of this transporter leads to hyperexcretion of these neutral amino acids and to intestinal malabsorption. Excretion of tryptophan metabolites kynurenine and N-methyl-nicotinamide is reduced. Plasma concentrations of the affected amino acids may be low normal or reduced. The inheritance is autosomal recessive. The hph2-deficient mouse has been postulated as a model for Hartnup disorder [17]. Affected persons may be asymptomatic, while some demonstrate pellagra-like photodermatitis or cerebellar ataxia due to a nicotinamide deficiency and respond well to the administration of nicotinamide [16].

13.2 Nomenclature

No.	Disorder	Amino acid	Tissue distribution	Chromosome	MIM
13.1	Cystinuria	cys, arg, lys, orn	intestinal, renal	2p21, 19q13.1	220100
13.2	Dicarboxylic aminoaciduria	glu, asp	renal	9p24	222730
13.3	Hartnup disorder	neutral amino acids	GI, renal		234500

13.3 Metabolic Pathways

Fig. 13.1. The transport of amino acids across the intestinal and tubular cells involves several steps, which are demonstrated schematically for a proximal tubular cell: AA, amino acid; BLM, basolateral membrane; BBM, brush border membrane; TBM, tubular basement membrane; 1, specific transporter at the luminal membrane; 2, passive efflux from cytosol into tubular lumen; 3, transport system at the basolateral membrane; 4, transport from peritubular site into cytosol; 5, energy production for electrolyte transport; 6, passive efflux via paracellular gaps. (Taken from Foreman, JW and Segal, S (1987) Fanconi syndrome. In: Pediatric Nephrology (eds. Holliday MA, Barratt TM and Vernier RC), pp 547–565, Williams and Wilkins, Baltimore, with permission to and modified by Brodehl J)



13.4 Signs and Symptoms

Table 13.1. Cystinuria

System	Symptoms	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Urinary	Urolithiasis	–	±	±	±	±
	Urinary tract infection	–	±	±	±	±
	Obstructive uropathy	–	±	±	±	±
	Renal insufficiency	–	–	±	±	±
Routine laboratory	Hematuria	±	±	±	±	±
	Leucocyturia	±	±	±	±	±
	Cystine crystals (U)	+	+	+	+	+
Special laboratory	cys (U)	↑↑	↑↑	↑↑	↑↑	↑↑
	arg, lys, orn (U)	↑	↑	↑	↑	↑
	cys, arg, lys, orn (P)	↓–n	↓–n	↓–n	↓–n	↓–n

Table 13.2. Dicarboxylic aminoaciduria

System	Symptoms	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Mental retardation	–	±	±	±	±
Special laboratory	glu, asp (U)	↑	↑	↑	↑	↑
	glu, asp (P)	↓	↓	↓	↓	↓
	pro (P)	n–↑	n–↑	n–↑	n–↑	n–↑

Table 13.3. Hartnup disorder

System	Symptoms	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Ataxia	±	±	±	±	±
Skin	Photodermatitis (pellagra-like)	±	±	±	±	±
Special laboratory	Neutral amino acids (U)	↑	↑	↑	↑	↑
	Indolic acids (U)	n-↑	n-↑	n-↑	n-↑	n-↑
	Neutral amino acids (P)	↓-n	↓-n	↓-n	↓-n	↓-n
	Neutral amino acids (stool)	n-↑	n-↑	n-↑	n-↑	n-↑

13.5 Reference Values

■ Plasma Amino Acids (μmol/l) (See also Chap. B)

Age	Arg	Lys	Orn	Cys	Glu	Asp	Ala	Phe	Val	Trp
Neonatal	22–139	68–286	20–134	46–130	27–168	5–44	144–459	27–84	62–232	27–71
Infancy	37–121	62–271	25–101	43–99	40–129	5–32	165–458	32–84	107–292	
Childhood	36–106	78–207	20–84	43–100	20–97	3–20	153–517	21–64	112–286	12–69
Adolescence	55–139	114–243	30–96	54–119	11–84	4–29	232–519	33–86	127–266	
Adulthood	32–88	99–249	32–88	34–67	10–67	<5	205–496	37–61	151–302	19–45

Ref. values=95% confidence range (see 1st edition, p. 252).

■ Urine Amino Acids (μmol/day) (See also Chap. B)

Age	Arg	Lys	Orn	Cys	Glu	Asp	Ala	Phe	Val	Trp
Neonatal	<2	1–92	<7	2–48	<15	3–24	14–85	<9	<8	
Infancy	<15	2–110	<9	2–41	<38	6–44	26–228	1–27	<20	
Childhood	<19	6–168	<7	4–54	2–38	15–87	37–312	1–53	<37	
Adolescence	<32	27–725	<20	17–201	3–56	22–209	59–584	9–115	6–66	
Adulthood	<77	79–1682	13–134	42–254	36	15	92–923	13–134	<102	41.4

Ref. values=95% confidence range.

13.6 Pathological Values/Differential Diagnosis

■ Plasma Amino Acids (μmol/l)

Disorder	Arg	Lys	Orn	Cys	Glu	Asp	Ala	Phe	Val	Trp
13.1	42–89	100–151	24–101	18–29			183–633	22–75	101–274	
13.2					25–87	<5				
13.2	81–107	168–208	68–122	17–35	22–24	<10	330–408	53–61	154–254	21–39

■ Urine Amino Acids (mmol/day)

Disorder	Arg	Lys	Orn	Cys	Glu	Asp	Ala	Phe	Val	Trp
13.1	0.13–11.54	0.77–21.84	0.19–5.69	0.56–54.04			0.06–0.24	0.02–0.07	0.01–0.11	
13.2					18.3±2.3	1.2±0.1				
13.3	0.02	0.11–0.32	0.02–0.04	0.03–0.09	0.3–0.5	<2	1.6–2.9	0.2–0.5	0.9–2.2	0.29–0.35

13.7 Loading Tests

Loading tests are not necessary for the diagnosis of amino acid transport disorders. However, pathophysiologically they may help in differentiating between different types of cystinuria by oral application of cystine and dibasic amino acids followed by analysis of plasma amino acids. The polyamines putrescine and cadaverine are produced intestinally, absorbed and excreted into the urine. Loading with dibasic amino acids will result in increased production of these polyamines [9, 10].

Oral loading with tryptophan in Hartnup disorder will lead to increased production of indole compounds which can be analysed in the urine.

13.8 Diagnostic Flow Chart

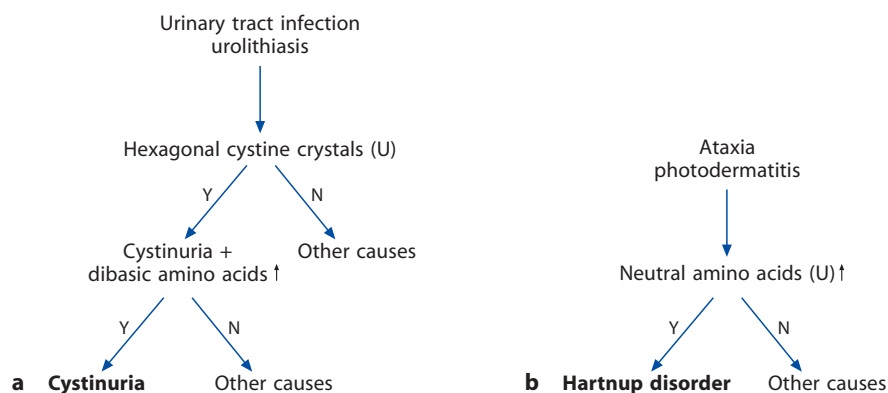


Fig. 13.2. Diagnostic flow charts for cystinuria (a) and Hartnup disorder (b)

13.9 Specimen Collection

Blood for the analysis of plasma amino acids, esp. cystine should be deproteinized immediately. Blood and urine spot specimens for the calculation of the percentage tubular amino acid reabsorption (%TAA) have to be taken within 1–2 h.

13.10 Prenatal Diagnosis

Prenatal diagnosis is not recommended in cystinuria or Hartnup disorder.

13.11 DNA Analysis

DNA analysis may be performed in cystinuria from leukocytes or fibroblasts (SSCP-based mutation identification) but is not necessary for diagnosis.

13.12 Initial Treatment

In cystinuria fluid intake should reach 3 l in children and approximately 4–5 l in adults during day and night. The objective of urine alkalization is to achieve a pH of 7.5.

In Hartnup disorder oral nicotinamide may prevent or resolve photodermatitis.

13.13 Summary/Comments

Rapid diagnosis of cystinuria in early childhood by urine screening, and in children or adults with nephrolithiasis with subsequent start of therapy, may prevent stone formation.

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